UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FERRING PHARMACEUTICALS INC., FERRING B.V., and FERRING INTERNATIONAL CENTER S.A.,

Plaintiffs,

v.

SERENITY PHARMACEUTICALS, LLC, and REPRISE BIOPHARMACEUTICS, LLC,

Defendants.

Case No. 1:17-cv-09922 (CM) (SDA)

SERENITY PHARMACEUTICALS, LLC, REPRISE BIOPHARMACEUTICS, LLC, and AVADEL SPECIALTY PHARMACEUTICALS, LLC,

Counterclaim-Plaintiffs,

v.

FERRING B.V., FERRING INTERNATIONAL CENTER S.A., and FERRING PHARMACEUTICALS INC.,

Counterclaim-Defendants.

Case No. 1:17-cv-09922 (CM) (SDA)

FINDINGS OF FACT, CONCLUSIONS OF LAW AND VERDICT

McMahon, C.J.:

The court, for its findings of fact after trial, conclusions of law and verdict:

I. FINDINGS OF FACT

A. The Parties

1. Serenity and Reprise

FF1. Reprise is a corporation organized under the laws of the State of New York, having its principal place of business at 120 North Main Street, Suite 400, New City, New York 10956. [Fein Affidavit ¶ 61.][1] Dr. Fein and Dr. Nardi are principals and equity partners in Reprise; Linda and Maria Cheng are also Reprise partners. Dr. Fein has a 44% ownership stake, and he gave Dr. Nardi an 18% interest in Reprise as his business partner. Reprise, in turn, holds a 10-11% ownership stake in Serenity. [Trial Tr. 421:9-24.]

FF2. Serenity is a corporation organized under the laws of the State of Delaware and has its principal place of business at 480 NE 30th Street, Unit 1807, Miami, FL 33137, and maintains a location at 122 Willow Street, Brooklyn, New York 11201. [Fein Affidavit ¶ 65.]

FF3. Serenity is the exclusive licensee of Reprise's intellectual property rights in desmopressin, including the patents at issue here. [PX-3[2], at Non-AGN0098020.] Serenity was formed to develop desmopressin products in conjunction with Reprise. [Fein Affidavit ¶ 59.]

FF4. Together, Serenity and Reprise are the owners of any intellectual property rights Dr. Seymour Fein – the Chief Medical Officer of Serenity, founding principal and controlling shareholder of Reprise, and the sole listed inventor of the patents-in-suit – has in the patents at

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[1] Unless otherwise noted, all references to "Affidavit" in this document refer to the direct testimony affidavits filed in preparation for trial in this case.

[2] All references to "PX-" in this document refer to documents listed on Counterclaimants' Exhibit List; all references to "DX-" refer to documents listed on Ferring's Exhibit List; and all references to "JX-" refer to documents listed on the parties' Joint Exhibit List, all filed along with the Pretrial Order in this case.

issue in this case. [PX-1, at ASR-FER000193133-36; PX-2, at ASR-FER000193150-51; Fein Affidavit ¶ 66.]

FF5. At the time of the original complaint, Allergan, a commercial partner of Serenity and Reprise, held all rights to the patents at issue in this lawsuit, which had been assigned to them by Reprise and Serenity. [PX-4, at AGN-FER000005051-56; PX-5, at AGN-FER000004984.] In 2017, Allergan terminated the parties' License, Transfer, and Development Agreement. [PX-7, at AGN-TM000001.]

FF6. Counterclaimants then entered into a commercial development agreement with Avadel. [PX-8, at ASR-FER00000514-92.] Through that agreement, Avadel became an exclusive sublicensee to the patents-in-suit. [*Id.*]

FF7. Avadel filed for Chapter 11 bankruptcy in February 2019. (*See In re: Avadel Specialty Pharmaceuticals LLC*, 1:19-BK-10248 (D. Del.).) Ferring reached a settlement with Avadel in May 2019, at which point Avadel was dismissed from this case and Ferring confirmed it would seek no discovery or testimony from Avadel. [D.I.[3] 500.]

2. Ferring

FF8. Ferring Pharmaceuticals Inc. is a privately held Delaware corporation with its principal place of business located in Parsippany, New Jersey. Ferring Pharmaceuticals Inc. is owned by Ferring Holding, Inc., which is owned by Ferring B.V. [D.I. 18 ¶ 1.]

FF9. Ferring B.V. is a Dutch private limited liability company having its registered office in the Netherlands. [*Id.* ¶ 2.]

FF10. Ferring International Center S.A. is a Swiss private company with its principal place of business in Saint-Prex, Switzerland. [*Id.* ¶ 3.]

[3] All references to "D.I." in this document refer to docket entries in this case, unless otherwise indicated.

FF11. Ferring (a term that will be used to refer to all Defendants collectively) engages in pharmaceutical research and development activities. [*Id.* at 4.]

3. The patents-in-suit and Person of Ordinary Skill in the Art

FF12. The patents-in-suit in this action are U.S. patents 7,405,203 (the '203 patent) and 7,579,321 (the '321 patent). The patents-in-suit are generally directed to the use of the drug desmopressin to treat various voiding disorders while reducing the risk that the patient develops hyponatremia, a potentially harmful side effect. The methods of treatment involve administering to a patient a pharmaceutical composition comprising a dose of desmopressin sufficient to achieve and maintain certain plasma/serum concentrations and/or urine osmolalities over a defined period of time. [Mayersohn Affidavit ¶ 32; Murray Affidavit ¶ 108.] The '321 patent is a continuation of the '203 patent. The sole inventor listed on the patents in suit is Dr. Fein.

FF13. A Person of Ordinary Skill in the Art ("POSITA") at the time of the invention would include an individual or a team of individuals, having, as his/her/their minimum qualifications, an M.D. or Pharm.D or Ph.D. degree in pharmacology, pharmaceutics, or other related discipline, with knowledge in the field of pharmacokinetics and pharmacodynamics, or an MD with experience in diagnosing and treating patients with voiding disorders.

B. Background Information: Pharmacology

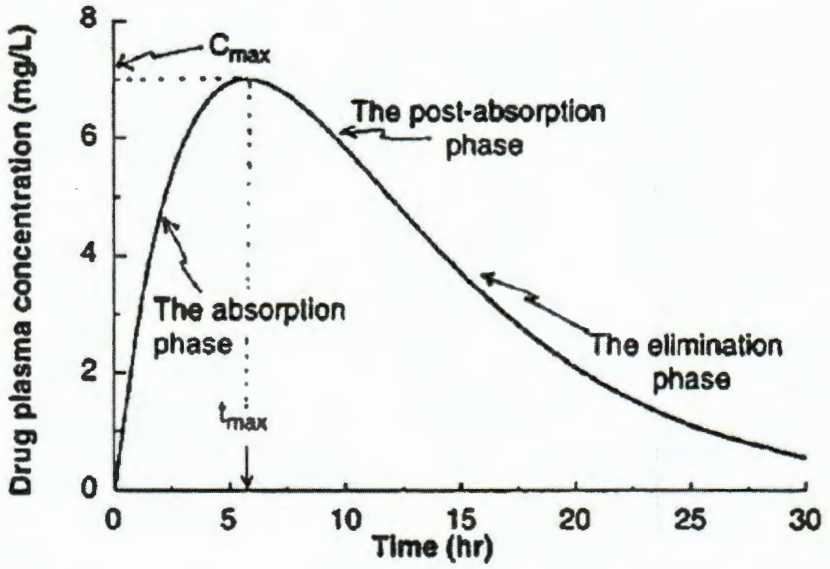
FF14. At a broad level, pharmacology is the study of chemical substances, such as drugs, that interact with the human body through chemical and biological processes. [Spaans Invalidity Affidavit ¶ 32.] It has two branches: pharmacokinetics and pharmacodynamics.

1. Pharmacokinetics

FF15. Pharmacokinetics is one branch of pharmacology that seeks to analyze the actions of the human body on a pharmaceutical drug compound. [Stipulated Fact ¶ 4.]

FF16. The time course of absorption of the drug into the bloodstream and the eventual clearance of the drug from the body is a pharmacokinetic measurement. [Stipulated Fact ¶ 5.]

FF17. In pharmaceutical drug development, researchers analyze many different pharmacokinetic parameters, including but not limited to the blood plasma concentration of the pharmaceutical drug absorbed into the bloodstream at different time intervals. This information can then be graphed as a function of time, as shown below:



[Spaans Invalidity Affidavit ¶ 34.]

FF18. As shown above, after a drug is administered to a subject, it is gradually absorbed into the bloodstream and the plasma concentration increases, reaches a maximum, and then returns towards the baseline. [*Id.* ¶¶ 35-36.]

FF19. The maximum plasma concentration achieved after administration of a drug to a subject is known as the C_{max}. [Stipulated Fact ¶ 6.] The time it takes to reach the C_{max} is known as the T_{max}. [Stipulated Fact ¶ 7.]

FF20. Total exposure is shown by the AUC, which is the total "area under the curve" of the plasma concentration graph. [Spaans Invalidity Affidavit ¶ 37.]

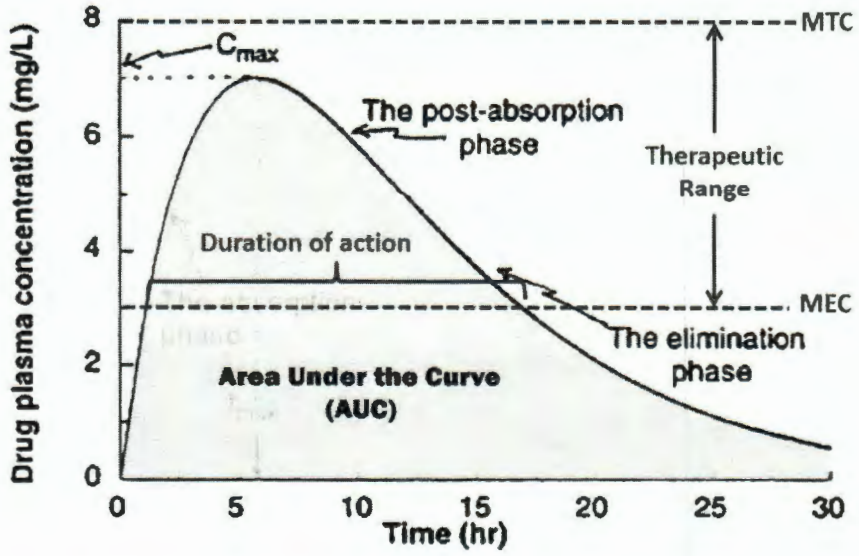
FF21. Bioavailability is defined as the fraction of the administered dose of a drug that is absorbed into the bloodstream. Bioavailability, like other pharmacokinetic parameters, may depend on the formulation, dosage form, and the route of administration. [Stipulated Fact ¶ 8; Spaans Invalidity Affidavit ¶ 37.]

FF22. Intravenous ("i.v.") administration of a drug is typically assumed to have 100% bioavailability because the drug is administered directly into the bloodstream. Other routes of administration, which rely on absorption into the bloodstream rather than direct injection, will have lower bioavailability. [*Id.*; Mayersohn Rebuttal Affidavit ¶ 36.]

2. Pharmacodynamics

FF23. Pharmacodynamics is another branch of pharmacology. It analyzes the pharmacological effect of a pharmaceutical drug on the body. [Stipulated Fact ¶ 9.]

FF24. With respect to the graph below, the pharmacodynamic parameters are represented by the "duration of action," the minimum effective concentration ("MEC"), and the minimum toxic concentration ("MTC").



[Spaans Invalidity Affidavit ¶¶ 41-42.]

FF25. The therapeutic range for a drug lies between the MEC and MTC, and the time that the blood plasma concentration remains within that therapeutic range (and thus is producing an effect) is known as the duration of action. [*Id.* ¶ 42.]

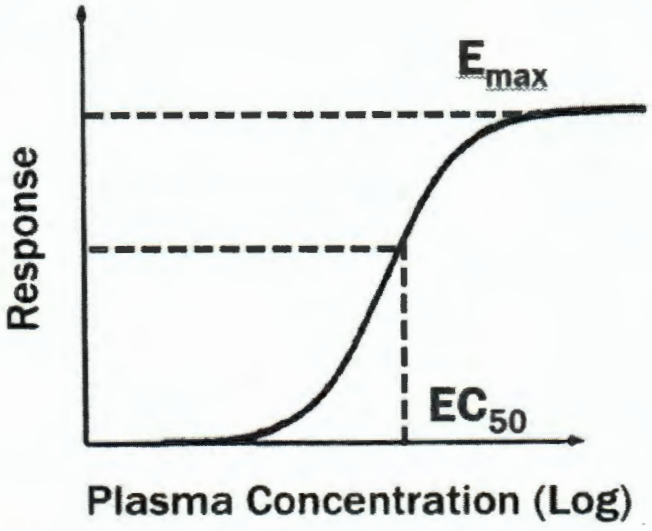
3. The relationship between pharmacokinetics and pharmacodynamics

FF26. Pharmacokinetic and pharmacodynamic events overlap, and the concentration of drug in the blood (or plasma) and the rate at which that concentration changes over time are driving forces for pharmacodynamic events following drug dosing. [Stipulated Fact ¶ 10.]

FF27. While the absolute dose administered affects the plasma concentrations, it is the plasma concentrations that determine the pharmacological response to the drug. [Stipulated Fact ¶ 11.]

FF28. With an understanding of the pharmacokinetics and pharmacodynamics of a particular formulation, drug developers can develop a dose response relationship and use this relationship to select doses and potential formulations, and target plasma concentrations to produce the desired effect to treat patients. Generally, in order for the dose response relationship to be useful in predicting how different formulations or routes of administration for a particular drug will behave, the underlying pharmacokinetic and pharmacodynamic data must be robust and accurate. [Spaans Invalidity Affidavit ¶ 44.]

FF29. An example of a dose response curve is shown below:



As can be seen above, the dose-response curve begins at zero plasma concentration and zero pharmacodynamic effect. As the plasma concentration of the drug increases, the pharmacodynamic effect also increases. [*Id.* ¶¶ 45-46.]

FF30. Typically, the relationship between the plasma concentration and pharmacodynamic effect is nonlinear. In other words, small changes to plasma concentrations at the lower end of the spectrum produce larger changes in pharmacodynamic effect, but small changes to higher plasma concentrations result in smaller changes in pharmacodynamic effect. This is because, at higher plasma concentrations, the drug is reaching its maximum effect (shown as E_{max} in the graph above) and the curve reaches this maximum effect asymptotically. [*Id.* ¶ 46]

FF31. The point labeled EC_{50} in the above graph refers to the plasma concentration that produces 50% of the maximum pharmacodynamic effect, a parameter that is useful in describing the potency of a particular drug. [*Id.* ¶ 47.]

4. Variability in pharmacokinetic and pharmacodynamic parameters

FF32. One issue that arises in evaluating pharmacokinetic and pharmacodynamic parameters for drug development is the variability in the observed data. Typically,

pharmacologists use two primary measures of variability – standard deviation and the coefficient of variation ("CV"). [*Id.* ¶¶ 49-50.]

FF33. The standard deviation is an expression of how far away the values in a particular data set are from the mean. Typically, approximately 68% of the values in a particular data set will fall within one standard deviation of the mean value. [*Id.* ¶ 49.]

FF34. The CV, also known as the relative standard deviation, is another measure of variability in a data set. The CV is the ratio of the standard deviation to the mean and is generally expressed as a percentage. The CV provides an indication of precision and repeatability. Typically, pharmacokinetics rely on the CV to provide variability information regarding pharmacokinetic data. [*Id.* ¶ 50.]

FF35. In drug development, a POSITA would consider data to exhibit high intra-subject variability if the CV is above 30% for a reasonable number of study subjects. [*Id.* ¶ 53; Mayersohn Rebuttal Affidavit ¶ 82.] Similarly, in drug development, a POSITA would consider data to exhibit high inter-subject variability if the CV is above 30%. [Spaans Invalidity Affidavit ¶ 53.]

FF36. A data set that repeatedly gives the same values would have a low standard deviation and low CV, and the individual values would be close to the mean. For example, if the data set were 49 and 51, the mean would be 50, the standard deviation would be 1, and the CV would be 2%. In contrast, if the individual numbers vary widely, the standard deviation and CV will be higher, and the values may not be close to the mean. If the data set were 0 and 100, the mean would still be 50, but the standard deviation would be 50, and the CV would be 100%. In the examples above, although the mean value is the same, it is only reasonably representative of

the actual values in the first example -- which is why, all things being equal, lower variability is preferable in drug development. [*See id.* ¶¶ 49-50.]

C. Desmopressin

FF37. Desmopressin is a synthetic analog of the hormone arginine vasopressin, which is produced by the posterior pituitary gland and regulates the body's retention of water. [Stipulated Fact ¶ 1.]

FF38. Desmopressin is a potent antidiuretic that binds to the V2 receptors in kidney cells, leading to increased reabsorption of water in the kidneys, which in turn results in more concentrated urine and decreased water excretion. [Murray Affidavit ¶ 23.] Desmopressin is used to treat a variety of voiding disorders, such as central diabetes insipidus ("CDI") (a specific type of diabetes where patients produce a lot of urine), primary nocturnal enuresis ("PNE") (bedwetting in children), and nocturia (disruption of nighttime sleep in elderly persons due to the need to urinate). [*See* JX-1-0013 at 1:28-33.]

FF39. Desmopressin is not a new drug. Indeed, it has long been used drug treatment for voiding disorders; Ferring has worked with desmopressin for over 45 years, having performed its first study with desmopressin in CDI[4] in 1971. Ferring marketed desmopressin as both an oral tablet (i.e., a tablet that is swallowed with water) and a nasal spray long prior to the year 2000; the oral tablet was marketed under the name DDAVP in the United States and MINIRIN in Europe. [JX-13-0014, JX-13-0019.]

FF40. One potentially adverse effect of desmopressin treatment is a condition called hyponatremia, which is an abnormally low concentration of sodium in the blood. [JX-1-0020 at

[4] Central diabetes insipidus (CDI) is caused by deficiency of arginine vasopressin (AVP), an antidiuretic hormone which acts on V2 receptors in kidney to promote reabsorption of free water.

16:29-33.] Side effects of desmopressin include hyponatremia, *i.e.*, low serum sodium levels, particularly in elderly patients. Symptoms of hyponatremia include nausea, headache, lethargy, and in severe cases, seizures and death. [Murray Affidavit ¶ 24.]

FF41. A POSITA would anticipate that different patients would respond variably to desmopressin. The source of such variability is explained, *inter alia*, by inherent differences in pharmacological or physiological sensitivity (*i.e.*, pharmacodynamic variability) and differences in bioavailability and pharmacokinetic parameters among patients. [Mayersohn Rebuttal Affidavit ¶ 45.]

D. The Pharmacokinetics and Pharmacodynamics of Desmopressin

FF42. Desmopressin formulations typically exhibit high variability, as can be seen by looking at the results of Ferring's CS021 study, which investigated the effects of 60, 120, and 240 μg doses of desmopressin administered in the form of an orodispersible tablet (a tablet that is placed in the mouth and that, instead of being swallowed, melts in the mouth). [JX-12.]

FF43. In that study, the mean C_{max} was 4.033 pg/ml, 9.577 pg/ml, and 19.044 pg/ml for the 60 μg, 120 μg, and 240 μg doses, respectively. [*See* JX-12-0065 at Table 9-2.] The standard deviations from the mean C_{max} in CS021 were 1.548 pg/ml, 7.123 pg/ml, and 15.003 pg/ml. [*Id.*] This results in a CV for the C_{max} numbers of 34.1%, 62.4% and 83.6% for the 60 μg, 120 μg, and 240 μg, respectively. [*Id.*]

FF44. The CS021 study states that: "The inter-subject variability of the desmopressin plasma concentration data . . . was considerably high, which is known from the large variability in absolute oral bioavailability of desmopressin." [JX-12-0068.]

FF45. The pharmacodynamic response (i.e., antidiuresis) for desmopressin exhibits similar variability. [Trial Tr. 1013:20-1014:9; Juul Non-Infringement Affidavit ¶ 6.]

FF46. For example, in Example 8, the mean durations of action as determined by urine osmolality were 20, 68, and 208 minutes for the 0.5 ng/kg, 1.0 ng/kg, and 2.0 ng/kg intravenous bolus doses administered over the course of two hours at the 400 mOsm/kg threshold, respectively. [*See* Vis Affidavit ¶ 55.] The standard deviations from the mean durations in Example 8 were 49, 113, and 85 minutes. This results in a CV for the durations of action of 245%, 168% and 41% for the 0.5 ng/kg, 1.0 ng/kg, and 2.0 ng/kg intravenous bolus doses. [*Id.*]

FF47. The Parties' experts agree that there is high variability within desmopressin's bioavailability. [Mayersohn Rebuttal Affidavit ¶¶ 37, 55; Spaans Invalidity Affidavit ¶ 81.]

FF48. Because of its high degree of variability, desmopressin doses are subject to both interpatient and intrapatient variabilities, and doses necessary to treat different voiding disorders and for different patient populations are different. [Mayersohn Rebuttal Affidavit ¶ 83; Verbalis Affidavit ¶ 30.]

FF49. Because of this variability in the pharmacokinetics and pharmacodynamics of desmopressin, it is not possible to predict with great accuracy the desmopressin plasma concentrations or durations of action for an individual subject. In other words, the same formulation with the same dose, given to different individuals (or even the same individual at different times), will produce different desmopressin plasma concentrations and durations of action. In one individual, administration may produce almost no desmopressin plasma concentration (and thus no duration of action), while in another individual, it may produce many times the mean C_{max} with a correspondingly longer duration of action. [Juul Non-Infringement Affidavit ¶¶ 8-14.]

FF50. Dr. Mayersohn, Serenity's/Reprise's expert, admitted on cross examination admitted that for any individual subject you cannot know, without testing that patient, whether

any given patient will respond to desmopressin in a manner that would get him/her within the claim limitations of the patents-in-suit. [Trial Tr. 38:22-39:10.]

E. The State of the Art - Dr. Nørgaard's Desmopressin Research

FF51. Dr. Fein acknowledges that "shortly after the introduction of desmopressin, literature appeared—published articles in peer reviewed journals—about new uses of desmopressin and certain side effects that might occur." [Fein Affidavit ¶ 12.]

FF52. Ferring presented evidence about two studies from the 1980s, both of which concluded that low doses of desmopressin administered in oral tablet form exhibited antidiuretic effects at low plasma concentration levels. [DX-98 (1986 study by T.D.M. Williams et al.); Trial Tr. 319:3-16 (discussing DX-121 (1985 study by Hammer)).]

FF53. Dr. Jens Peter Nørgaard, a urologist who served as a consultant for Ferring since the 1980s, and who became a Ferring employee in 1996, also believed that desmopressin could be effective in treating voiding disorders at low plasma concentrations. The court credits Dr. Nørgaard as a witness generally. Specifically, I credit his testimony that, beginning as early as 1996, he recognized that desmopressin exhibited an antidiuretic effect at very low plasma concentration levels.[5] He counseled against the use of high doses of desmopressin, at Ferring and in writing, and favored research into the use of lower doses. [Trial Tr. 727:13-728:4; 966:14-967:19; Nørgaard Affidavit ¶¶ 43-46.] Unlike with Dr. Fein, there is a clear written record of his interest in the subject and of his views over time.

[5] This is in part because desmopressin is a replacement for the hormone vasopressin, which is typically present at around 1-2 pg/mL. As Dr. Nørgaard testified, "since desmopressin is a replacement, it cannot be a surprise that we would aim for these levels. The problem was, and still remains to be, that we are not able to detect the low plasma levels on the assays." [Trial Tr. 967:11-16.]

FF54. At trial, Dr. Fein admitted that the idea of antidiuresis being achieved with low doses based on low plasma concentrations of desmopressin was known in the prior art through the Hammer and Williams references and the Nørgaard articles prior to 2001. [Trial Tr. 320:9-12.]

1. Dr. Nørgaard's 1996 Article

FF55. In 1996 – shortly before he joined Ferring as Director of Therapeutic Area in Urology, [Nørgaard Affidavit ¶ 39], Dr. Nørgaard published an article titled, *"Hyponatremia in Patients with Nocturnal Enuresis Treated with DDAVP* [desmopressin]." [DX-2; "1996 article".] In that article, Dr. Nørgaard stated that high doses of desmopressin were undesirable because they would "prolong the duration of pharmacologic action and might increase the risk of water intoxication [hyponatremia]," [DX-2-0003], and further noted that no studies had yet been performed to assess the incidence of hyponatremia at different doses of desmopressin. [Nørgaard Affidavit ¶ 47.]

2. Dr. Nørgaard's 1999 Article

FF56. In his early years as a Ferring employee, Dr. Nørgaard published several articles and presentations in which he highlighted that desmopressin has maximal antidiuretic effect at low plasma concentrations and that lower doses of what he described as a "very potent drug [that] acts for a long time," [DX-3-0003; Trial Tr. 729:14-24], were preferable to higher doses being prescribed.

FF57. For example, in 1999, Dr. Nørgaard published an article on the PK/PD effects of an oral tablet form of desmopressin. In the article, Nørgaard sought to address what he viewed as a misconception, by personnel at Ferring and elsewhere, that the way to deal with patient nonresponse to desmopressin was to increase the dose. Dr. Nørgaard's article questioned this idea. He explained that low plasma concentrations of desmopressin would produce an

antidiuretic effect in most patients, and that increasing the dosage did not result in additional antidiuresis, but simply increased the drug's duration of action longer than necessary. [Nørgaard Affidavit ¶¶ 49-52; DX-3-0002-3.]

FF58. In the conclusion of the article, Dr. Nørgaard stated that "Small plasma concentrations of desmopressin or AVP are required; even poor absorption of desmopressin may be sufficient to obtain the required level of plasma desmopressin." [DX-3-0002.] He further stated, "Some patients may still experience a wet bed despite maximal antidiuretic effect of desmopressin, and increasing the dosage could result in no clinical effect, but instead may increase the risk of an undesired increase in duration of action." [*Id.*]

FF59. While the article deals principally with children who wet the bed at night (PNE), it noted that elderly patients experiencing nocturia were more sensitive to desmopressin than children were, suggesting that nocturia patients should be treated with lower, not higher, doses of desmopressin. [*Id.*]

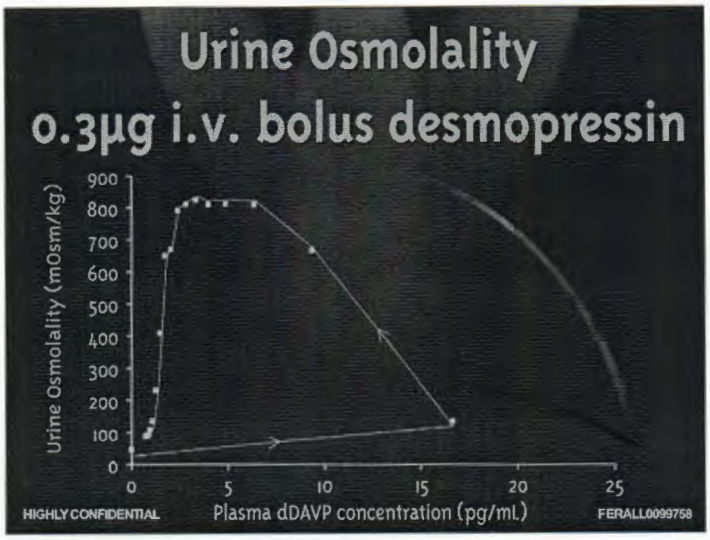
3. Dr. Nørgaard's 1999 ICCS Presentation Slides

FF60. That same year, Dr. Nørgaard gave a presentation at an International Children's Continence Society conference in Denver, Colorado – an organization that Dr. Nørgaard had helped to found. [DX-147; Trial Tr. 960:3-8; Nørgaard Affidavit ¶ 53.]

FF61. During the presentation, Dr. Nørgaard presented research that showed that desmopressin has a maximal antidiuretic effect at far lower plasma concentrations than were previously thought to be clinically effective — as low as under 3 pg/mL. [DX-4-0012.] This indicated to Dr. Nørgaard that in upcoming research programs, research should explore the efficacy of lower doses of desmopressin – which he believed sufficient to achieve antidiuresis – rather than trying to achieve high plasma levels of the drug. He also noted that increasing dosage

could give rise to hyponatremia because it would extend the drug's duration of action. [DX-4-0021; Nørgaard Affidavit ¶¶ 56-57.]

FF62. The presentation included a slide with a graph (a hysteresis curve) that reflects the relationship between plasma concentration of desmopressin and antidiuretic effect, as shown by urine osmolality (i.e., urine concentration):



[DX-4-0012.] As shown in the graph starting in lower left corner at zero, the 0.3 µg of desmopressin was administered intravenously into a healthy volunteer and (following the arrow on the graph pointing to the right) the plasma concentration immediately rose to the C_{max} around 16 pg/mL. At that point, there was a slow increase in the urine osmolality as the kidneys begin to react (following the arrow up and back to the left), then a continued effect of desmopressin on urinary osmolality of 800-900 mOsm/kg all the way down to plasma concentrations of approximately 3 pg/mL. After that, the urine osmolality dropped, and the individual started producing urine again. The leveling off of the urine osmolality at a maximum effect of just more than 800 mOsm/kg – a level at which it remained until the plasma concentration decreased below about 3 pg/ml – is significant in that that it shows that very low plasma concentrations result in a strong antidiuretic effect with a very high concentration of urine. [Nørgaard Affidavit ¶¶ 54-56.]

FF63. Based on these data, Dr. Nørgaard concluded in his slides that "The need for high plasma levels of desmopressin is overestimated." [DX-4-0021; Nørgaard Affidavit ¶¶ 56-57.]

4. Dr. Nørgaard and Ferring's Minirin Rollover—1999 through early 2000

FF64. When Dr. Nørgaard was first employed by Ferring back in 1996, he was tasked with (1) finalizing ongoing nocturia studies for the oral desmopressin tablet (DDVAP/Minirin) that Ferring had been marketing for some time, and (2) identifying follow-up candidates to the oral tablet through either new formulations or new molecules. As part of the latter task – which was of some urgency, as Ferring's patents on its oral tablet were soon to expire – Dr. Nørgaard hoped to justify "more accurate dose and exposure," most particularly in elderly nocturia patients. [Nørgaard Affidavit ¶ 42.]

FF65. On the "new formulations" track, Ferring went into development with a company to create a rapidly dissolving oral formulation of desmopressin (an "orodispersible tablet" or ODT) that would melt in a patient's mouth. This was referred to as the NewMin project. This project began in or about 1999, in Copenhagen, where Dr. Nørgaard was located. At that time, Dr. Fein was a Ferring consultant working in the United States, but not on any projects related to desmopressin. [Fein Affidavit ¶¶ 17-24.]

FF66. As part of this project, Ferring considered, at least as early as 1999, the use of an orodispersible sublingual tablet. [DX-125-0001.]

FF67. In November 1999, Dr. Nørgaard became Head of Clinical Research in Urology at Ferring. Ferring intended to seek approval for a new formulation of desmopressin to treat CDI, PNE, and nocturia and needed to do clinical studies that would, *inter alia*, investigate appropriate doses for each of these indications. Dr. Nørgaard decided to take this opportunity to explore his

idea that lower-than-conventional doses of desmopressin would be effective, especially in nocturia patients. [Nørgaard Affidavit ¶ 44.]

FF68. Study 45A07-39 – of which Dr. Nørgaard was the Medical Officer – was designed to study the bioavailability and pharmacokinetics of desmopressin in men aged 55-75. The study was actually initiated in 1996, while Dr. Nørgaard was at the University of Aarhus, but the final clinical trial report was not finished until December 16, 1999. [DX-6; Nørgaard Affidavit ¶ 58.] The study showed that a dose of desmopressin in the elderly resulting in a plasma level of 4-5 pg/mL achieved maximum antidiuretic effect. [*Id.*]

FF69. On page FERALL0038593 of the final report, dated December 16, 1999, a graph presented the plasma concentration over time for administration of desmopressin both during daytime (morning) and at nighttime (evening). [DX-6-0032.] The study showed that a single dose of 200 µg MINIRIN oral tablet produced sufficient antidiuresis to permit the subjects to attain a night's sleep.

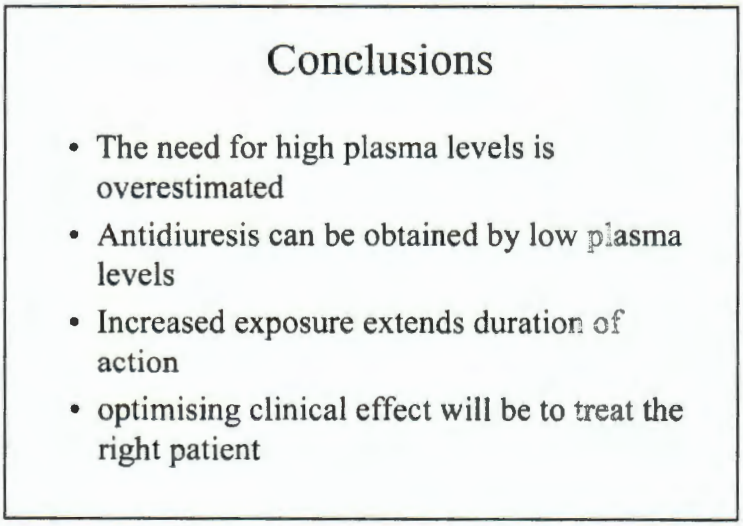
FF70. The 200 µg MINIRIN was very poorly absorbed by the patients (who represented a target population for nocturia) and generated the same antidiuretic effect as a much smaller, 2 µg i.v. administration of desmopressin, and those levels remained "identical" for about six hours.[6] [DX-6-0039.] This demonstrated that an essentially maximum antidiuretic effect was being reached with plasma levels as low as 4 pg/mL, which was in line with the hysteresis curve from Dr. Nørgaard's ICCS presentation. [DX-6-0057 (reporting maximum mean plasma concentration of 4.42 pg/mL for nighttime administration of 200 µg oral tablet).] The study demonstrated that, in general, very low plasma concentrations of desmopressin are expected to

[6] Equivalent to 100 or 140 mcg orodispersible tablets administered sublingually. This is because the oral tablet has lower bioavailability than the orodispersible tablet. [JX 10-0002; DX 19-0015, 45.]

be sufficient for the desired clinical response: antidiuresis for the number of hours related to sleep. [Nørgaard Affidavit ¶ 62.]

FF71. Thereafter, in early 2000 (before Dr. Fein was involved at the desmopressin project at Ferring), Dr. Nørgaard gave an internal presentation to senior management at Ferring with the title "The Minirin rollover." [DX-7.] A "rollover" is a Danish expression meaning a complete change in the strategy. Nørgaard wanted Ferring to change its strategy as it focused on marketing for nocturia by shifting to lower doses of desmopressin, which would be beneficial in avoiding hyponatremia. [*Id.*; Nørgaard Affidavit ¶¶ 65-68.]

FF72. Specifically, in his presentation, Dr. Nørgaard included Figure 1 from his 1999 paper on nonresponders; the hysteresis curve from his ICCS presentation, showing that maximal antidiuresis occurs even at plasma concentrations as low as 3 pg/mL; and the information from the 45A07-39 study, showing the maximum plasma concentrations below 5 and 10 pg/mL, as well as the duration of action being six hours. [DX-7-0006-07, 10, 12-13.] In the presentation, Dr. Nørgaard again concluded that "The need for high plasma levels is overestimated," and that "Antidiuresis can be obtained by low plasma levels," such as the plasma levels shown in the 45A07-39 study below 5 pg/mL:



[DX-7-0023.]

FF73. Dr. Nørgaard made similar statements about the risk of hyponatremia from higher doses of desmopressin to regulatory authorities in early 2000. [*See* DX-29-0001 ("After some discussion, Jens Peter Nørgaard (JPN) gave his presentation on clinical and safety issues. He stated clearly that increased exposure would lead to increased duration of action, and that this could eventually lead to increased water intake in the morning and risk for hyponatremia.").]

FF74. Dr. Nørgaard and his Ferring colleague, Dr. Thomas Senderovitz, also filed a report with European regulators in October 2000 which stated that: "Tablets are comparable to i.v. injection regarding the antidiuretic effects during the first 6 hours after administration." [DX-8-0010.] The report concluded that: "Increased doses of dDAVP (and hence increased plasma concentrations) result in prolonged duration of pharmacological action – not necessarily more pronounced antidiuretic effects (in terms of urine production or urine osmolality changes)." [DX-8-0003.]

FF75. That same month, Ferring initiated studies to refine its understanding of the dose/response relationship of desmopressin, so that the company could target specific durations of action with particular doses with greater accuracy. The goal of the study was to establish a PK/PD model for desmopressin in nocturia, so that Ferring could choose the best doses, and appropriate durations of action, to pursue in subsequent clinical studies of the NewMin formulation. [Nørgaard Affidavit ¶¶ 72-76.] EMF Consulting France was hired to do this study; Nørgaard's colleague at Ferring, Thomas Senderovitz, designed the model. [DX-55-0001; Nørgaard Affidavit ¶ 73.]

FF76. A key takeaway from this study was to be the prediction of an EC_{50} value for desmopressin – that is, the plasma concentration at which desmopressin provides half of its maximum antidiuretic effect (its half-life). [*Id.* ¶ 74.]

FF77. The study, which was not completed until February 2002, revealed that the halflife of desmopressin in the bloodstream was about 0.7 pg/mL. [*Id.* ¶ 92.] Ferring used this EC_{50} value to estimate that the C_{max} for 10 µg of the orodispersible tablet is 0.7 pg/mL, "in the same order of magnitude as the EC_{50} values for urinary production, calculated from [EMF] simulations." [DX-21-0019.]

FF78. It is apparent from the foregoing that others besides Dr. Fein – including specifically Dr. Nørgaard at Ferring – hypothesized that desmopressin is a very potent drug that has maximal antidiuretic effects at low plasma concentrations and that lowering the dose of desmopressin from the doses in use could effectively treat voiding disorders, including but not limited to nocturia, while lessening the danger of hyponatremia by shortening the drug's duration of action. It is also apparent that Ferring and Nørgaard were actively studying the issue and raising the question publicly in the mid-1990s. While the same thought may have occurred to Dr. Fein during the 1990s, there is absolutely no credible evidence in the record that he took a single step to study the issue, to discuss it is publicly, or to do anything else that might have turned any such hypothesis into an invention. Ferring, by contrast, actively explored the low plasma concentration hypothesis through extensive research projects on desmopressin, both to improve dosing of the oral tablet and to find new formulations of the drug, as early as 1990. [*See Ferring B.V., et al. v. Allergan Inc., et al*, No. 12-cv-2650 (PKC), 2019 WL 6183501, at *3 (S.D.N.Y. Sept. 27, 2017) [hereinafter "2012 Action Findings of Fact"] (Findings of Fact and Conclusions of Law, ¶¶ 17-18).]

F. Desmopressin and Dr. Fein's Time at Ferring

FF79. Dr. Fein began consulting with Ferring in late 1994. He worked primarily on the development of fertility drugs. [Fein Affidavit ¶¶ 17-18.]

FF80. In late 1997, Dr. Fein joined Ferring as an employee. He stayed on as an employee for only a year, after which he, at his request, transitioned back to consulting status. [*Id.* ¶¶ 19-21.]

FF81. Dr. Fein did no work on desmopressing prior to 2001 and did no work on desmopressin in early to mid-2001. [*Id.* ¶ 24.]

FF82. The date Dr. Fein has assigned for the commencement of his work on desmopressin has varied during the course of this and other litigations concerning the various low plasma concentration desmopressin patents. I do not credit Dr. Fein's testimony that he began consulting about desmopressin in July 2001; the credible evidence indicates that Dr. Fein did not even meet the key players at Ferring who were deeply immersed in desmopressin research until a brief "meet and greet" during a trip that he made to Copenhagen in late August 2001 – a trip he made principally to work on a non-desmopressin-related project. Dr. Fein's contemporaneous time records indicate that he spent about 1.5 hours on August 28-29 (1 hour on August 28 and .5 hour on August 29, during a trip to Ferring headquarters in Copenhagen) on the "Desmopressin Nocturia Program" – as opposed to 76.5 hours of work on a program concerning a different drug known as Degarelix. [DX-122-0015-16.] Dr. Fein spent a total of 214.5 hours consulting for Ferring during the month of August 2001, so he was obviously not much involved with desmopressin at that point. It is quite clear that he was in Copenhagen to meet and work with the Degarelix team. Significantly, both Drs. Nørgaard and Senderovitz were working on

Degarelix as well as desmopressin, so Fein's brief encounters with them may well have dealt with Degarelix in substantial part. [Trial Tr. 323:22-328:15; 390:24-397:7.]

FF83. Dr. Fein claims to have explained his ideas about low dose desmopressin and sublingual administration of the drug to Dr. Ronald V. Nardi, Ferring International's Corporate Vice President for Research and Development, earlier in August 2001 (prior to his trip to Copenhagen). Dr. Nardi, a key witness in this case, was not called to testify by Serenity/Reprise; I surmise that is because he testified at the recent Allergan trial before my colleague Judge Castel and was found greatly lacking in credibility. [*See* 2012 Action Findings of Fact ¶¶ 89-93.]

FF84. Dr. Nardi has a financial interest in Reprise and Serenity. He is, therefore, within the control of the Counterclaimants. I know of no impediment to Counterclaimants' producing him for examination at trial, especially as he testified only a few months go before Judge Castel. Therefore, I will treat Dr. Nardi as a missing witness, and assume that his testimony would not be favorable to Counterclaimants' position in this lawsuit.

FF85. In the *Ferring v. Allergan* trial (No. 12-cv-2650) ("the 2012 Action"), Dr. Fein testified that he conveyed his discoveries regarding desmopressin to Dr. Nardi in an oral conversation in August 2001. He claims to have explained to Dr. Nardi that his invention was two-fold:

> Firstly, that desmopressin was more potent and that lower doses would be appropriate particularly for this new clinical indication of nocturia in an elderly population where you wanted to confine the drug effect to just the nighttime hours, four to six hours, at most eight hours, and having that effect dissipate before the patient awakened in the morning and began drinking fluids, coffee, tea, juice. But in order to use a low dose, the oral route of administration was not very suitable because desmopressin is a peptide, meaning it's a small protein. Proteins and peptides get digested when taken orally, and so I knew from the literature that the average bioavailability of the oral desmopressin tablet was .12 percent, meaning on average only about 1/800th of the drug in the tablet got

> absorbed into the bloodstream, but that could vary tenfold or greater from dose to dose and patient to patient, and the variability was just as bad as the high dose, because you just could not predict what the blood level would be after a given dose and how long the antidiuretic effect would last.
>
> So, I said this new dosage form, the orodispersible tablet, provides an opportunity to avoid the oral route of administration if it were adapted to be placed under the tongue. That's called a sublingual route of administration, and what it means is that the drug is dissolving and being directly absorbed into the bloodstream through the capillary bed under the tongue. That's a type of what is called transmucosal route of administration or transmucosal absorption.

[Fein Affidavit ¶ 34.]

FF86. The first documented notation indicating that Dr. Fein was consulting about desmopressin is dated September 10, 2001. [PX-102]. On this day, Dr. Fein wrote a memo to Olivier Delanoy – the head of marketing at Ferring in the United States – about the cost of the clinical program for oral desmopressin to treat adult nocturia in the United States. [Trial Tr. 450:16-23.]

FF87. Dr. Fein stated that he had "only recently and in a cursory fashion" begun to "review the Desmopressin Nocturia FDA briefing document and summary of EU regulatory questions." [PX-102.]

FF88. Among other observations Dr. Fein made in his memo, he said, "the new, rapidly dissolving sublingual tablet may be preferable depending on its pharmacokinetics." [*Id.*]

FF89. Dr. Fein was not the first person at Ferring to have this idea. At trial, Dr. Fein admitted that Ferring was already working on the development of the orodispersible desmopressin dosage form well before he got involved in working with desmopressin. [Trial Tr. 515:1-4.] Documentary evidence dating from 1999 – again, well before Dr. Fein was involved in desmopressin at Ferring – confirmed the same. [DX-125.] At that time, Jorgen Wittendorf, project team leader for the NewMin team, noted discussions "on a sublingual tablet easily

dissolvable" with Ferring's marketing team and the possibility of conducting a feasibility study. [DX-125-0001.]

FF90. During 2001 and early 2002, Ferring (in the person of Thomas Senderovitz) designed and carried out a study to examine the bioavailability of Zydis for a potential NewMin formulation (the orodispersible formulation). The study was designated CS004. [DX-13-0001; Nørgaard Affidavit ¶ 83.]

FF91. The study was discussed at the August 30, 2001 meeting of the NewMin team, at which Dr. Fein was not present. [DX-83-0001; Trial Tr. 378:11-19.]

FF92. Dr. Fein was not deeply involved in the design of the CS004 study, the final protocol for which was completed in December 2001. [Nørgaard Affidavit ¶ 87.]

FF93. Dr. Fein alleges that the CS004 study design was modified over the last few months of 2001 to incorporate "his" idea about sublingual administration. [Fein Affidavit ¶¶ 36-37.] The mode of administration used in the CS004 study did change from supralingual (on the tongue) to sublingual during the fall of 2001; and while Ferring had discussed the possibility of sublingual administration at least two years earlier, it appears that Dr. Fein's views on that subject may have had something to do with the choice of sublingual over supralingual administration.

FF94. The bioavailability of the orodispersible form as determined by CS004 is based on oromucosal administration generally, and there is no evidence in the record that sublingual versus supralingual administration changes the bioavailability of the rapid dissolving orodispersible tablet. [DX-15-0002; Trial Tr. 400:3-401:13; 1011:4-1012:4.]

FF95. DX-89 is a PowerPoint presentation given by Dr. Nardi to Ferring's Board of Directors on October 11, 2001 that provides a summary of all of Ferring's development work

related to a variety of development programs. The document specifically references sublingual orodispersible tablet ("ODT"). Dr. Fein's name is not mentioned on the document. The only thing that allegedly connects this to Dr. Fein is Dr. Fein's testimony (1) that Dr. Nardi made this presentation to the Ferring Board on October 11; and (2) that Dr. Nardi specifically included mention of sublingual administration because he was invested in Dr. Fein's discoveries. Unfortunately for Dr. Fein and Counterclaimants, Dr. Fein's testimony about anything that Dr. Nardi did at a Ferring Board meeting – and even more so, about why Dr. Nardi may have done it – is inadmissible and so will not be considered. [Trial Tr. 453:4-454:25.] Moreover, assuming arguendo that Dr. Nardi did speak about sublingual administration of an ODT to Ferring's Board in October 2001, the record demonstrates that Ferring scientists were considering this route of administration as early as June 1999 [*see* DX-125], and there is no basis other than Dr. Fein's inadmissible testimony to link the presentation to anything Dr. Fein said or did.

FF96. DX-89, which does not mention Dr. Fein, does not raise the inference that Dr. Fein played any significant role in shaping Ferring's desmopressin program, let alone that the program centered on Dr. Fein's ideas and inventions. [DX-89-0010.]

FF97. Dr. Fein began working with the desmopressin research team in the fall of 2001. He was not deeply involved in the bioavailability study of the ODT – known within Ferring as CS004 – the final protocol for which was completed in December 2001. [Nørgaard Affidavit ¶ 87.]

FF98. The results of the CS004 study were available by March 22, 2002. They showed that the mean bioavailability of Ferring's orodispersible formulation of desmopressin was about 0.3%, which is about double the mean bioavailability of the oral tablet (at the same doses). [JX 10-0002; DX 19-0045.]

FF99. That same month, Drs. Nørgaard and Senderovitz prepared a report to submit to European regulators as part of an application for "Part B" status for the new desmopressin ODT. The report [DX-15] summarized what the previous studies had shown: that while patients preferred to take a pill by mouth, the bioavailability of an oral tablet was low compared to intranasal administration (a nasal spray). The use of an ODT would "maintain the benefits of the oral administration route" while increasing absorption, and consequently the bioavailability of the drug. [DX-15-0002.] This would allow prescribers to cut the dose of desmopressin in half. [DX-15-0004.]

FF100. In their presentation, Drs. Nørgaard and Senderovitz stated that Ferring was looking at ways to lower dosage even further, "to reduce the duration of antidiuretic action and thereby increase the risk/benefit ratio, especially in the elderly." [*Id.*] The report also advised the regulators that, with a bioavailability of 0.3%, and knowing that a 200 mcg dose of the ODT yielded a C_{max} of approximately 14 pg/mL, it was possible to estimate that a 20 mcg dose (a dose lower than was prescribed) of the ODT would yield an expected plasma level of about 1.5 pg/mL – which would be enough to generate maximal or near-maximal antidiuresis. [DX-15-0004-05.]

FF101. The clinical development plan referenced in DX-15 next contemplated a study to investigate the PK and antidiuretic effect of five low doses of desmopressin and placebo in an ODT administered to healthy nonsmoking male volunteers. [DX-16.] This study was designated CS007. The doses of the ODT proposed for this protocol were 10, 20, 40, 80 and 160 mcg. Dr. Fein admitted that he had no involvement in the selection of doses and that the doses were based on the EMF study, of which he had no involvement. [Trial Tr. 521:2-23.]

FF102. CS007 was never conducted because the production delays at the supplier meant that the full range of doses for the ODT were unavailable to run the study. [Nørgaard Affidavit ¶ 103; Trial Tr. 941:9-13.]

FF103. The ideas meant to be tested in CS007 were examined in an alternate study, CS009. In that study, desmopressin was to be administered intravenously in amounts that approximated the values for the ODTs that were to have been administered in CS007; that got Ferring around the production delay problem. The doses chosen were 30, 60, 125, 250 and 500 ng administered as a constant rate intravenous infusion over two hours. [DX 18-0004.] Again, these doses were based on the EC_{50} value of desmopressin[7] obtained from the results of a modeling project Ferring initiated in October 2000 – well before Dr. Fein allegedly revealed his "invention" to Dr. Nardi. [Nørgaard Affidavit ¶ 102.]. The lowest dose was intended to check the hypothesis that it would produce clinically significant antidiuresis; the highest doses were included in order to develop a full dose-response curve.

FF104. The CS009 protocol was drafted over the period prior to June 6, 2002, the date of the protocol. Dr. Fein does not allege in his affidavit testimony that he had anything to do with the initial drafting of the CS009 protocol; he admits that he did not see a draft until early June 2002. [Fein Affidavit ¶ 40.]

FF105. However, Dr. Fein was involved in helping to conduct, as opposed to design, the CS009 study. Dr. Nørgaard first contacted Dr. Fein about the CS009 study on May 31, 2002, when Dr. Fein and other medical directors in various countries were advised that their assistance would be needed in operating clinical studies that were being initiated as part of a high-speed development program for the ODT. [DX-59-0001.]. Dr. Fein was asked by Dr. Thomas

[7] In this instance, the EC_{50} value is the value at which desmopressin exerts half of its maximum antidiuretic effect.

Senderovitz, by email dated June 3, whether he would conduct the clinical studies, including the CS009 study, in the United States. [DX-61-0001.]

FF106. Between June 4 and June 6, Drs. Nørgaard, Senderovitz, and Fein corresponded about Senderovitz's request. Dr. Fein at first told his European counterparts that Dr. Nardi had said that Dr. Fein's U.S. group would not be involved in the ODT program until it reached Phase 3 studies; since the CS009 study was a Phase 1 study, that meant Dr. Fein first refused to conduct the study. [DX-62]. The next day, however, Dr. Fein indicated that he would be eager to participate in the clinical development program. [*Id.*]

FF107. On June 7, 2002, Harriet Hansson of Ferring sent Dr. Fein a copy of the CS009 protocol that had been developed in Copenhagen. [Nørgaard Affidavit ¶ 108.] Dr. Fein "marked it up" by deleting the last sentence in the document that read "If doses can be decreased, this might turn into a clinical benefit as a diminished risk for patients to develop hyponatremia." Dr. Fein did so because he believed it was premature for a phase one study to be speculating on clinical outcomes and the study was premature to relate it to therapeutic use. [Trial Tr. 349:21-350:19; 353:6-21.] In fact, the sentence he deleted indicated that other Ferring scientists had already hypothesized that lower doses might lessen the risk of hyponatremia – an idea that Dr. Fein would eventually attribute to himself.

FF108. Dr. Fein also converted the doses selected by Ferring Copenhagen (30 ng, 60 ng, 125 ng, 250 ng, and 500 ng) into ng/kg form (0.45 ng/kg, 0.9 ng/kg, and 1.8 ng/kg). Dr. Fein admitted at trial that this was merely a change of the form in which the dose was described, and was not a change in the dose (that is, 30 ng in the hypothetical 70kg study subject is equivalent to .45 ng/kg; 60 ng is equivalent to .9 ng/kg, and so forth). [Trial Tr. 358:1-19.]

FF109. Over the objection of the Ferring Copenhagen team, Dr. Fein and the U.S. team modified the protocol for CS009 for testing purposes by reducing the number of doses that were to be tested from five to three – eliminating the top two doses (250 ng and 500 ng). Going from five doses to three did not generate any data that would not have been available from the original design of the five-dose study; it only yielded less data – specifically, data that Dr. Nørgaard thought would be useful in showing the dose-response relationship over a range of doses, thereby allowing Ferring to select doses to achieve specific durations of action for each voiding disorder for which desmopressin was used (CDI, PNE, nocturia). [Nørgaard Affidavit ¶¶ 110-111.] Dr. Fein refused to discuss these changes with Dr. Nørgaard [DX-66] and the study that was conducted by Dr. Fein in the United States conformed to his wishes. [Fein Affidavit ¶¶ 45-46; Nørgaard Affidavit ¶¶ 110-111.]

FF110. Ferring eventually decided to design a new study, CS011, that tested what they had envisaged for CS009. [*Id.*] CS011 became part of Ferring's Clinical Development Plan. [DX-67-0006-8.]

FF111. CS009 was performed in the U.S. in 2002, with preliminary results available in October 2002, and a final clinical study report executed in 2005. The data confirmed that low doses and low plasma levels of desmopressin shortened the duration of action but did not alter clinical efficacy.

G. The Ferring Patent Application and Dr. Fein's Departure From Ferring

FF112. Ferring filed its Great Britain ("GB") application on May 7, 2002. The application did not name any inventors. [JX-3-0001.]

FF113. The GB application included eleven examples, Example 1-7 and Comparative Examples 1-4. [JX-3-0026-31.]

FF114. Dr. Fein was not involved in any of the studies underlying Examples 1-6 or Comparative Examples 1-4.

FF115. Example 7 of the common specification is based on Ferring's clinical study designated CS004, with which Dr. Fein had only the minimal involvement described above. [FF 92-93; DX-88; Trial Tr. 332:4-335:25.]

FF116. More or less contemporaneously with this filing, Dr. Fein was asked by Dr. Nardi to provide Ferring's patent counsel with an inventorship memo. That memo was drafted on May 14, 2002. [PX-26.]

FF117. In the memo, Dr. Fein claimed that his contribution to the patent for which Ferring was applying was "a sublingual, transmucosal route of delivery rather than an oral one with ingestion of the drug into the gastrointestinal tract." [PX-26-0001] Dr. Fein recognized that the "project team at FIC [Ferring International]" – of which he was not a member – was planning the Zydis experiments using "an alternative oral dosage form of desmopressin consisting on [sic] an oro-dispersible wafer which spontaneously dissolved in the mouth and could be swallowed without water." [*Id.*] Significantly, Dr. Fein attributed the idea of sublingual absorption of the drug to Dr. Nardi as well as to himself.

FF118. In this memo, Dr. Fein did not claim that he and Dr. Nardi had contributed the idea of lower doses of desmopressin, or of specific dosage forms that would result in any particular PK or PD parameters, although he stated their purported belief that the use of sublingual administration would result in "more rapid absorption (shorter T_{max}), higher peak blood levels for a given dose (greater C_{max}), higher systemic bioavailability for a given dose (greater AUC or area under the curve), decreased variability of desmopressin blood levels (absorbed dose) among individual patients for a given dose, more consistent pharmacodynamic

duration of action among patients for a given dose, [and] the potential to create effective doses of Zydis tablets which contained less desmopressin than oral tablets and, therefore, increased patient safety." [PX-26-0001-02.] However, none of these hypotheses has ever been substantiated. [Trial Tr. 401:4-13; 1011:4-1012:4.] And with the exception of increased patient safety, none of these hypotheses is claimed in the patents-in-suit.

FF119. Dr. Fein indicated in the inventorship memo that he had first discussed his ideas with Dr. Nardi in early November 2001, in advance of a trip to Copenhagen in mid-November 2001. Because there is no record of any such meeting in Copenhagen in November 2001, I find that this was a mistake on Dr. Fein's part. Because Dr. Fein joined the desmopressin projects in or about September 2001 (no earlier), I conclude that he must have had this "informal hallway-based conversation" sometime in August 2001 – not in July 2001, as he eventually testified. [Trial Tr. 320:13-21.] However, the fact that Dr. Fein could make such a significant error in timing in a document as important as the inventorship memo suggests to this court that his involvement with desmopressin research at Ferring prior to November 2001 was far less than he now makes it out to be.

FF120. In this memo, Dr. Fein states, "During our discussions at that meeting, Dr. Nardi and I recognized that the dissolution characteristics of Zydis when placed in the mouth could be utilized to create a sublingual, transmucosal route of delivery rather than an oral one with ingestion of the drug into the gastrointestinal tract." [PX-26-00001; Trial Tr. 379:7-381:20.]

FF121. In reliance on Dr. Fein's Inventorship Memo, Ferring's patent counsel concluded that Dr. Fein was entitled to be attributed as one of several inventors on the proposed patent – along with Nilsson, Senderovitz, Lindner, Wittendorf and Nardi – because Drs. Fein and Nardi

had come up with the idea of "sublingual transmucosal *absorption*[8] [as] the route of choice" for the ODT. [DX-93-0002 (emphasis added).]

FF122. On September 20, 2002, Ferring filed a Patent Cooperation Treaty ("PCT") application, PCT/IB02/04036 ("PCT '036"), listing Dr. Fein among the inventors of the patent. [PX-59.]

FF123. I find DX-93 an admission by Ferring that Dr. Fein was involved in the ODT desmopressin project from the fall of 2001 until his termination in the fall of 2002, and that Drs. Fein and Nardi were, at least in part, jointly responsible for contributing the idea of sublingual administration of the ODT as the route of choice for the administration of desmopressin in the CS004 design. [DX-93-002.]

FF124. I find PX-26 to be an admission by Dr. Fein that he was not the sole inventor of (1) sublingual administration (if only because he originally claimed that Dr. Nardi was co-inventor of that idea, though the credible evidence indicates that Ferring had considered it earlier); or (2) the idea that low doses of desmopressin would result in low plasma concentration that would nonetheless have antidiuretic effect (a hypothesis that can be documented to Dr. Nørgaard and others years before there is any credible evidence that Dr. Fein was interested in desmopressin), or (3) any specific dosage formulation that was being tested by Ferring (dosages having been selected by Dr. Senderovitz). There is clear and convincing evidence in the record that all three these ideas were being considered by Ferring employees for use in tests with the orodispersible tablet form. [DX-140; DX-125.]

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[8] Sublingual absorption of desmopressin requires sublingual administration, but sublingual administration does not necessarily result in sublingual absorption. [2012 Action Findings of Fact ¶ 13.]

FF125. Although Dr. Fein was a consultant to Ferring, and all of the above work was performed as part of his consultancy and on behalf of Ferring, Dr. Fein had never been asked to sign a consulting agreement that would have required him to acknowledge that any intellectual property he developed while working for Ferring was the property of Ferring. [Fein Affidavit ¶ 23.]

FF126. In or about November 2002, Dr. Fein was asked to sign a new consulting agreement that would have remedied this rather glaring omission on Ferring's part. He refused, and his consultancy with Ferring was terminated within hours. [Fein Affidavit ¶¶ 51-52.]

H. The Applications for the Patents-in-Suit

FF127. Just two weeks later, on November 21, 2002, Ferring received a letter from an attorney, William Speranza, on behalf of Dr. Fein. The letter said:

> It has been explained to us by Dr. Fein that, while serving as a consultant to Ferring in November, 2001, he invented a significant improvement to Ferring's desmopressin technology, more particularly a sublingual, transmucosal route of delivery which affords a number of advantages in the efficacy and safety of desmopressin administration, including enabling the effective use of formulations having reduced concentrations of desmopressin. We are further advised by Dr. Fein that Ferring has recognized the importance of this advance, and has properly acknowledged Dr. Fein's inventorship of it, by including the invention, along with certain other subject matters, in a PCT patent application naming Dr. Fein as one of the designated inventors.
>
> . . . We have carefully reviewed with Dr. Fein the nature of his consulting arrangement with Ferring in the applicable period . . . and have readily concluded under applicable law that no such assignment or obligation of assignment governs this invention and the patent rights therein.
>
> . . . [B]ecause the PCT patent application filed by Ferring includes subject matters in addition to Dr. Fein's invention, which subject matters were apparently invented by one or more Ferring employees, Ferring is exercising control over the proceedings on the application. Given Dr. Fein's ownership rights, we are assuming that Ferring recognizes that its activities in this regard . . . are as constructive trustees of the rights of Dr. Fein, and that those rights will be thoroughly and adequately protected and preserved throughout the course of proceedings in the PCT application and the filing and prosecution of any national phase applications.
>
> [PX-15-2753-54.]

FF128. Speranza does not mention any involvement in this "invention" by Dr. Nardi – in contrast to what Dr. Fein had said in his inventorship memorandum of six months earlier. I find that this was because Dr. Nardi was a Ferring employee, who owed a fiduciary duty to Ferring and whose work on any and every project belonged indisputably to Ferring. [2012 Action Findings of Fact ¶¶ 89-93.]

FF129. On April 9, 2003, Patricia Barclay, General Counsel of Ferring, responded to Speranza by indicating that Ferring had "taken the decision to drop the feature 'adapted for sublingual administration' from its PCT, and advising that it would be filing a modified PCT application by May 7, 2003 that would drop Dr. Fein as a listed inventor. Barclay advised Speranza that Ferring had concluded that the dropped feature was not novel over the prior art. [PX-15-2766.]

FF130. At no point prior to Ms. Barclay's decision had either Dr. Fein or Speranza indicated in any written document – including without limitation Dr. Fein's inventorship memo or Speranza's initial letters – that Dr. Fein claimed to be the "inventor" of anything other than the sublingual route of administration of desmopressin. In particular, there was no assertion that he claimed to have invented any "low dose" or dosage form that resulted in any plasma concentration or duration of action.

FF131. On April 17, 2003, Speranza emailed Barclay and, while indicating that Dr. Fein had "no fundamental problem" with Ferring's decision to drop the sublingual delivery feature from its PCT and to drop Dr. Fein as an inventor as a result, went on to say, "We do point out that Dr. Fein is also the inventor of the associated low dosage possibilities enabled by the sub-lingual administration route. We do not see that this was ever specifically claimed in the UK application, and we assume that Ferring is not pursuing that subject matter in the planned PCT

filing. . . . Dr. Fein is planning to himself proceed with pursuing patent protection covering the sub-lingual administration route and the associated low dosage possibilities enabled by same which he invented . . . with the understanding that Ferring relinquishes any ownership claims thereto." [PX-15-2769.]

FF132. Barclay, responding on behalf of Ferring, immediately took the position that, "The low dosages possibilities enabled by the sublingual administration route are already available in the public domain as exemplified by the enclosed abstract from Anne M Fjellestad-Paulsen's doctor's thesis published in 1996. This is the reason as we have explained that we will not be pursuing this claim." [PX-15-2772.] Attached was a copy of the pertinent portion of the thesis, which was legended "sublingual administration," and which said, "An adequate antidiuretic effect of 10-12 h with a gelatin-based sublingual lozenge containing 20 μg dDAVP [Ferring's desmopressin] has been reported (Grossman *et al.*, 1980) in diabetes insipidus patients. A similar effect was seen in 18 diabetes insipidus patients with a sublingual tablet containing 30 μg (Laczi *et al.*, 1980)." [PX-15-2775] 20 mcg and 30 mcg are very low doses of desmopressin; and this document demonstrated that low dosage possibilities based on sublingual administration were indeed "available in the public domain" at the time of the correspondence.

FF133. On May 6, 2003, Dr. Fein filed PCT '436 with the USPTO, listing himself as the sole inventor. At the time, Dr. Fein claimed that his invention was "a pharmaceutical dosage form of desmopressin adapted for sublingual administration." That invention comprised .5 ng to 20 mcg desmopressin. [JX-4-0004-05.]

FF134. On May 7, 2003, Ferring filed modified PCT '368 in the UK, reflecting its April 9, 2003 decision to remove Fein, Nardi and Senderovitz as inventors. [DX-103; PX-15.]

FF135. Ferring's modified PCT '368 led to the issuance of two patents – the '429 and '654 patents – which are PX-24 and PX-25 respectively.

FF136. Dr. Fein filed a patent application ('100) on November 12, 2003 as a continuation-in-part of PCT '463. [DX-31.]

FF137. Dr. Fein added certain new disclosures to the '100 application that were not present in his earlier PCT '463 application, including Example 8 and Figures 1-9. [JX-9-0005 to JX-9-0054.]

FF138. Example 8, which was added to the common specification in Dr. Fein's PCT '463, is essentially a copy of the protocol Ferring's CS009 study, which was based on Dr. Senderovitz's and Dr. Nørgaard's dose selection and targeted plasma concentrations predicated on the 0.7 pg/mL EC_{50} value and the 0.3% mean bioavailability of Ferring's orodispersible formulation. [DX-20-0016 to DX-20-0017; DX-22-0012 to DX-22-0013.]

FF139. Both CS009 and Example 8 implement the same water loading of 1.5% of body weight, use the same urine sample collection scheme, and use the same sequence of study days. [DX-20-0006 to DX-20-0007; JX-1-0022 to JX-1-0023 at 20:50-21:16; DX-22-0003 to DX-22-0004.] The doses are essentially identical and utilize the same units: ng/kg. Whereas Ferring's CS009 study implemented doses of 0.45, 0.9, and 1.8 ng/kg, Example 8 uses rounded doses of 0.5, 1.0, and 2.0 ng/kg, which are insubstantially different from the Ferring doses, and Dr. Fein was in possession of the preliminary results from CS009 before he left Ferring. [Trial Tr. 360:11-17; DX-20-0006; JX-1-0022 at 20:39-49; DX-22-0003.] CS009 and Example 8 also propose nearly identical urine osmolality cutoffs for duration of action: 125, 200, and 400 mOsm/kg for CS009, and 150, 200, and 400 mOsm/kg for Example 8. [DX-20-0040; JX-1-0023 at 21:22-26; DX-22-0037.]

FF140. Dr. Fein included data from the CNF Desmo PK 200301 study in the '100 application as Example 8, and claimed it was his sole inventive work, even though it was derived from Ferring's work to which Dr. Fein made no substantive inventive contributions. [Vis Affidavit ¶¶ 26-27; DX-20-0016 to DX-20-0017; DX-22-0012 to DX-22-0013.]

FF141. During prosecution of the patents, Dr. Fein relied heavily on Example 8 to demonstrate that the inventions were patentable; and eventually – after rejections for, *inter alia*, obviousness and anticipation [JX-8-0152 to JX-8-0162] – the patents-in-suit were allowed because of Example 8. The patent examiner specifically cited as the basis for allowing the patents the Affidavit of Dr. Thomas Berl, [JX-7-0312], who argued for the patents on the basis of the data in Example 8. [*See* JX-7-0004 to JX-7-0012, JX-7-0050 to JX-7-0056; JX-8-0081 to JX-8-0084.]

FF142. The Examiner then issued the Notice of Allowance and stated that "While the prior art teaches desmopressin compositions and the use for voiding postponement, the art previously recognized the necessary dose to be significantly higher than that which is instantly administered, such that administering a 'low' dose as claimed is unobvious and presents an unexpected result." [JX-8-0487 to JX-8-0488.] The patents-in-suit are not limited by dose.

FF143. Dr. Fein's application led to the issuance of three divisional patents – the patents in suit in this action and the '761 patent. [JX-1; JX-2; DX-113.] The '203 patent is titled "Pharmaceutical Compositions Including Low Dosages of Desmopressin." Dr. Fein is the sole inventor and Reprise is the assignee. The '321 patent is also titled "Pharmaceutical Compositions Including Low Dosages of Desmopressin," and lists Dr. Fein as the sole inventor and Reprise as the assignee. It is a continuation of the '203 patent.

I. The Common Specification

FF144. The patents-in-suit share a common specification. While the substance of the common specification is identical, the location of text may differ by column and line across the patents in suit. [Stipulated Fact 26.]

FF145. Counterclaimants assert that "certain portions of the common specification are similar to portions of the GB application from which the patents-in-suit claim priority," but that statement is disingenuous. Large portions of the two documents are identical, and I specifically find that Dr. Fein copied them, virtually verbatim – which necessarily means that he had either taken copies of Ferring's proprietary documents with him or they were provided to him by Dr. Nardi. It is not necessary to decide which of those two things occurred. It is only necessary to say that Counterclaimants' proposed finding of fact 219 is specifically found by this court to be contradicted by clear and convincing evidence in every respect.

FF146. The majority of the common specification is directed to an orodispersible formulation of desmopressin and methods for making such a formulation. [*See, e.g.*, JX-1-0014 to JX-1-0020 at 4:20-16:15, Examples 1-7, Comparatives Examples 1-4.][9]

FF147. Examples 1 through 7 and Comparative Examples 1 through 4 were present in Ferring's GB application and relate specifically to work done at Ferring during the period when Dr. Fein was a Ferring consultant; he was not consulting on desmopressin except when the work done on Example 7 was performed. [*Compare* JX-1-0021 to JX-1-0022 at Examples 1-7, Comparative Examples 1-4 *with* JX-3-0026 to JX-3-0031 at Examples 1-7, Comparative Examples 1-4.]

[9] For ease of reference, Ferring cites to the '203 patent [JX-1] when referring to the common specification. The same disclosures are in the '321 patent [JX-2] at different column and line numbers.

FF148. When Dr. Fein filed PCT '463 on May 6, 2003, he changed the title from "Pharmaceutical Formulations" (which appeared in Ferring's GB application) to "Pharmaceutical Compositions Including Low Dosages of Desmopressin," and added certain disclosures. [*Compare* JX-3 *with* JX-4.]

FF149. Dr. Fein then filed the '100 application on November 12, 2003 as a continuation-in-part application of PCT '463. [JX-1-0013 at 1:8-13.] In doing so, Dr. Fein added certain new disclosures to the common specification that were not present in PCT '463. [*Compare* JX-4 *with* DX-31.]

FF150. The common specification (incorporating the added disclosures from PCT '463 and the continuation-in-part sections from the '100 application) states that the invention is directed to pharmaceutical compositions including low dosages of desmopressin for treatment of certain human diseases. [JX-1-0013 at 1:18-21.]

FF151. The common specification recognizes that desmopressin was already commercially available as of its filing date, and that desmopressin "is commonly prescribed for voiding postponement, incontinence, primary nocturnal enuresis (PNE) and nocturia, among other indications, including central diabetes insipidus." [JX-1-0013 at 1:28-33.]

FF152. The common specification recognizes that desmopressin has been administered in the art intravenously, subcutaneously, intranasally, and orally. [JX-1-0013 at 1:34-35.]

FF153. The common specification includes a table of what is presented as "Currently, approved labeling" for recommended desmopressin doses for various indications and routes of administration. [JX-1-0013 at 1:49-65.] It states that maximum plasma concentrations of desmopressin following these recommended doses "would be approximately 20-30 pg/mL." [JX-1-0013 at 1:66-2:2.] For instance, the common specification states that "For the desmopressin

oral tablet with only 0.1-0.15% bioavailability, a standard dose of 200-400 mcg would . . . produce a peak plasma/plasma/serum level of 20-30 pg/mL . . . ." [JX-1-0013 at 2:2-5.] The common specification, however, states that "Lower dosages are preferable if the same desired effect could be produced." [JX-1-0013 at 2:19-20.]

FF154. The common specification states that "It has also been unexpectedly discovered that low doses and plasma/plasma/serum levels of desmopressin are pharmacologically active and can achieve desired therapeutic efficacy." [JX-1-0014 at 3:40-43.]

FF155. The common specification states that the "daily dosage of desmopressin" will generally be from 0.5 or 1 μg to 1 mg per dosage form. [JX-1-0014 at 4:1-3.] Since 1 mg is 2000 times more than .5 μg, these are extraordinarily broad ranges. It also states that "Comparatively lower doses (e.g., lower dosages relative to the dosages above or provided in the art) are also specifically contemplated, for example from 0.5 ng to 20,000 ng, preferably 0.05 mcg (50 ng) to 10 mcg (10,000 ng), and more preferably 0.1 mcg (100 ng) to 2000 ng." [JX-1-0014 at 4:5-9.]

FF156. The common specification includes a new section added by Dr. Fein titled "Low Dosage Analysis and Applications." [JX-1-0020 to JX-1-0021 at 16:16-17:29.] The common specification states that:

> As indicated above, doses and plasma/plasma/serum concentrations of desmopressin from 5 to 40% of the current recommended doses and resulting plasma/plasma/serum levels are therapeutically effective and in some cases safer for certain disease conditions such as CDI, PNE, and additional clinical indications requiring pharmacological concentration of the urine.

[JX-1-0020 at 16:18-24.] However, the common specification specifically states that the invention is directed to particular plasma/plasma/serum desmopressin concentrations – not limited to particular doses. [JX-1-0020 at 16:46-50.] The listed plasma concentrations range from

about 0.1 pg/mL to about 10 pg/mL, a one hundred-fold increase in the plasma concentration, and preferably from about 0.5 pg/mL to about 5.0 pg/mL. [JX-1-0020 at 16:46-50.]

FF157. The "Low Dosage Analysis and Applications" section of the common specification goes on to state its reliance on existing art with respect to desmopressin formulations and routes of administration:

> These amounts and ranges of desmopressin *may be administered by any method known in the art*, including, without limitation, intravenous (bolus, infusion); subcutaneous (bolus, infusion, depot); intranasal; transmucosal (buccal and sublingual, e.g., orodispersible tablets, wafers, film, and effervescent formulations; conjunctival (eyedrops); rectal (suppository, enema)); transdermal (passive via patch, gel, cream, ointment or iontophoretic); or intradermal (bolus, infusion, depot) as outlined below. Additionally, pharmaceutical compositions that contain desmopressin in an amount that provide[s] the above plasma/plasma/serum desmopressin levels may be prepared by the above methods and using the above carriers, *or any other method known in the art.*

[JX-1-0020 at 16:51-64 (emphases added).]

FF158. According to the common specification, these dose ranges "can produce appropriate antidiuretic effect when administered by various routes as in the examples below:

Route of Administration	Effective Daily Dose Range
Intravenous (bolus and infusion)	0.5 ng-2000 ng
Subcutaneous (bolus, infusion, depot)	0.5 ng-2000 ng
Intranasal	0.1 mcg-20 mcg
Transmucosal including buccal and sublingual (orodispersible tablets, wafers, film and effervescent formulations), conjunctival (eyedrops), rectal (suppository, enema)	0.1 mcg-20 mcg
Transdermal (passive via patch, gel, cream, ointment or iontophoretic)	0.05 mcg-10 mcg
Intradermal (bolus, infusion, depot)	0.05 mcg-10 mcg

[JX-1-0020 to JX-1-0021 at 16:65-17:15.] The section concludes by noting that administration of low doses of desmopressin "can be an effective treatment regimen for clinical indications" and that one may also create specific formulations that may "enhance absorption and increase [] systemic bioavailability." [JX-1-0021 at 17:16-29.]

FF159. The Examples in the common specification include examples of three desmopressin formulations: an orodispersible tablet (the product that Ferring was testing while Dr. Fein was a consultant), a conventional oral tablet (a product that Ferring had sold in the marketplace for many years), and a conventional intravenous formulation (used in testing because it introduced the drug directly into the bloodstream and maximizes bioavailability). [JX-1-0021 to JX-1-0026 at Examples.]

FF160. Comparative Example 1 discloses an intravenous desmopressin solution that was "conventionally prepared." [JX-1-0021 at Comparative Example 1.] Comparative Examples 2 and 3 disclose a conventional desmopressin oral tablet formulation containing 200 µg or 100 µg of desmopressin, respectively. [JX-1-0021 to JX-1-0022 at Comparative Examples 2 and 3.]

FF161. Comparative Example 4 discloses another Ferring clinical study designed to test the bioavailability of the conventional oral tablets disclosed in Comparative Examples 2 and 3. [JX-1-0022 at Comparative Example 4.] Comparative Example 4 reports a mean C_{max} of 13.2 pg/ml and 15.0 pg/ml after an oral dose of 2x100 µg and 1x200 µg, respectively. [JX-1-0022 at 20:26-33.]

FF162. Examples 1 through 6 disclose two different orodispersible tablet formulations containing 200 µg, 400 µg, or 800 µg of desmopressin. [JX-1-0021 at Examples 1 and 4 (200 µg), Examples 2 and 5 (400 µg), and Examples 3 and 6 (800 µg).] Examples 1 through 6 include the same active ingredient (desmopressin) and excipients, but the amount of excipients used in

Examples 1 through 3 differs from the amount of excipients used in Examples 4 through 6. [*Compare* JX-1-0021 at Examples 1-3 *with* JX-1-0021 at Examples 4-6.]

FF163. Example 7 provides mean (not individual) pharmacokinetic data for the orodispersible tablets of Examples 4 through 6. [JX-1-0022 at 19:63-20:9.] This is an important feature, because everyone agrees that individual response to desmopressin varies widely – a fact amply borne out in the various studies that are part of the record in this case – which makes it difficult to extrapolate, from mean data, whether any individual patient for any particular disease indication will achieve the claimed PK and PD features at any particular dose.

FF164. CS004, the actual clinical trial study reporting the C_{max} values set forth in Example 7, reported the coefficient of variation for the mean C_{max} values of the 200, 400, and 800 µg oral dispersible tablets at 55.4%, 77.1%, and 94.9% respectively. Serenity and Reprise's own expert, Dr. Mayersohn, testified that these coefficients of variation are considered high. [Trial Tr. 53:4-5.] He further testified that with a coefficient of variation around 40%, due to the high inter- and intrasubject variability, it would be impossible to say whether a given individual would achieve a maximum plasma concentration of less than 5 pg/mL or 10 pg/mL for these doses. [Trial Tr. 1172:21-1174:14.] He testified that due to the variability, it would be a "distant possibility" when there is 47% variability in C_{max}. [Mayersohn Rebuttal Affidavit ¶ 83]

FF165. Further, the mean plasma concentration data reported in Example 7 was collected in healthy subjects, not patients suffering from the diseases claimed in the patents, who might well have different pharmacological responses to desmopressin. [Trial Tr. 561:19-563:16; Spaans Invalidity Affidavit ¶ 109.]

FF166. Example 7 also administered the intravenous formulation from Comparative Example 1 as a bolus dose. [JX-1-0022 at 19:28-32.] Example 7 does not report mean maximum

plasma concentration ("C_{max}") data for the intravenous bolus dose and instead only reports the mean volume of distribution at steady state, mean clearance, and mean elimination half-life. [JX-1-0022 at 19:64-67.] For the orodispersible tablets from Examples 4, 5, and 6, Example 7 reports a mean C_{max} of 14.25, 30.21, and 65.25 pg/ml, respectively. [JX-1-0022 at 20:2-4.] Example 7 also does not disclose the standard deviation or coefficient of variation for these mean C_{max} values.

FF167. As noted above, Dr. Fein was not actively involved either in designing or in carrying out this study, except to the extent of suggesting that the orodispersible tablet be administered sublingually as opposed to supralingually, as the study design had originally proposed. [*See supra* FF ¶¶ 79-143.]

FF168. Example 8 was not present in Ferring's GB application or in PCT '463 and was added by Dr. Fein in the '100 application. [*Compare* JX-3 *with* JX-4 and DX-31.]

FF169. Example 8 reports the results of a clinical study that involved five male and three female healthy volunteers. These eight volunteers were administered escalating doses of intravenous desmopressin that was infused at a steady rate over the course of two hours. [JX-1-0022 at 20:39-44.] The subjects discussed in the clinical study in Example 8 were between 18 and 40 years old and were dosed initially with 0.5 ng/kg, then with 1.0 ng/kg, and finally with 2.0 ng/kg, with a forty-eight-hour washout period between each dosing. [JX-1-0022 at 20:39-49.]

FF170. The basis for Example 8 is a study run by Dr. Fein's company, CNF Pharma. However, Dr. Fein and his CNF colleagues did not design that study. The clinical study protocol for the CNF study is essentially a copy of the protocol for a Ferring clinical study called CS009. As was found above, Dr. Fein did not design the CS009 protocol; in his capacity as a consultant to Ferring, he carried out that study on behalf of Ferring before he performed the study that

underlay Example 8. He thus had the results of the CS009 study protocol in his possession prior to the time that CNF ran "its" study. [Trial Tr. 419:1-17.]

FF171. At the Allergan trial, Judge Castel found that the CNF in CNF Pharma stands for Cheng, Nardi, and Fein. [*See* 2012 Action Findings of Fact ¶¶ 92-93.] The court takes judicial notice of this finding. The fair inference to be drawn therefore is that Dr. Nardi – Ferring's Corporate Vice President for Ferring's international research and development – was involved in a competing venture with a former Ferring consultant who was using Ferring's proprietary study designs and data for his own purposes.

FF172. Example 8 includes a summary of the results of the study and includes the urine osmolality and urine output results for each subject in Tables 1-6 and Figures 1-9 of the common specification. [*See generally* JX-1-0023 to JX-1-0026 at 22:19-27:3; JX-1-0004 to JX-1-0012 at Figures 1-9.]

FF173. The common specification states that the results of Example 8 "confirm the low-dose hypothesis . . . and provide an empirical basis for further clinical studies in patients to evaluate low doses of desmopressin for such conditions as primary nocturnal enuresis, adult nocturia, incontinence, and central diabetes insipidus." [JX-1-0026 at 27:4-8.] In addition, the common specification states that Example 8 "demonstrates that desmopressin can produce this essential antidiuretic effect at much lower doses and lower blood concentrations than previously thought." [JX-1-0026 at 27:48-51.] The common specification theorizes that "This may be adequate to produce the desired therapeutic effects for existing and potential new clinical indications for desmopressin." [JX-1-0025 to JX-1-0026 at 26:67-27:3.]

FF174. Example 8 is the only example in the common specification that provides pharmacodynamic information (i.e., the duration of action for antidiuresis). [*See generally,* JX-1; Spaans Invalidity Affidavit ¶ 71.]

FF175. The only example in the common specification that could embody the full scope of the functional claims is Example 8. According to Serenity and Reprise, Example 8 "established that the threshold desmopressin blood concentration sufficient to produce an anti-diuresis effect was much lower than the concentrations typically achieved in prior art practice." [DX-35-0003.][10] However, Example 8 – a study of 8 participants – who received a bolus i.v. injection with a bioavailability of 100% of desmopressin over two hours – reports only pharmacodynamic data related to urine osmolality, which purports to show (but does not in fact show) a duration of action of low doses of desmopressin from four to six hours.

FF176. Though the patents state that, "The pharmacodynamic duration of action was also proportional to the dose with the 1.0 and 2.0 ng/kg doses providing durations of four to six hours," the four to six-hour duration of action set forth in Example 8 and claimed in the patents was never calculated based on the specified protocol. Dr. Fein admitted as much. [Trial Tr. 420:13-16.] He testified that the four to six-hour duration of action claimed in the patent were "clinical, or target, ranges," rather than being the result of any actual analysis derived from the data. [Trial Tr. 507:16-19; 508:9-14.] Dr. Fein's testimony is not credible insofar as he claims that the pharmacodynamic range "aligns with the data," because he admitted that the study CNF conducted did not provide any information about the pharmacokinetic/pharmacodynamic relationship of low does and duration of action as stated in the protocol. [Trial Tr. 420:17-23]

[10] It's important to note that the patents-in-suit don't claim "*an*" anti-diuretic effect. They claim a blood plasma concentration level of 10 pg/mL or lower for four to six hours while reducing the risk of hyponatremia.

FF177. When the duration of action is actually calculated using the method set out in the protocol described in Example 8 – which is what the patent discloses to a POSITA – the examples teach a duration of action far lower than four to six hours. The mean urine osmolality data from the data in Example 8 is misleading because it censors individuals for whom the desmopressin treatment showed too little, or too much, of an antidiuretic effect. When calculating the mean duration of action as the patent teaches, both the mean durations of action for the 0.5 ng/kg and the 1.0 ng/kg administrations were well below the value of four to six hours. [Vis Affidavit ¶ 59.] For the .5 ng/kg dose, only two of the eight individuals showed any duration of antidiuretic effect at all. For the 1 ng/kg dose, seven of the eight people studied did not meet the functional limitations of the claim. [Trial Tr. 118:2-119:12.]

FF178. For the 2-nanogram-per-kg dose, which represents a dose of desmopressin already in the prior art, [Trial Tr. 1181:23-1182:8], three of the eight individuals were censored because they never dropped below the threshold level at the end of six hours, suggesting to a POSITA that the mean duration of action might exceed six hours. [Vis Affidavit ¶ 59.] Example 8 explains that "Subjects with no 'end' of action, with respect to the definition were censored at the time their urinary output returns to baseline (exceeds 10 mL/min) and/or the time where the over hydration procedure stopped." [JX-1-0023 at 21:34-38.] The data therefore contains subjects who either did not void or were no longer participating in the study based on three consecutive urine volumes greater than 10 mL/min. Example 8's reporting of mean osmolality data "aligning" with clinical ranges therefore combines heterogenous statistical materials while purporting to divine a linear trend.

FF179. Example 8 also fails to report any serum sodium levels, which is a key parameter used to measure hyponatremia. A POSITA would not be able to diagnose hyponatremia in the

absence of serum sodium levels. [Trial Tr. 874:5-16.] Although the common specification states, "Safety and tolerability were excellent" [JX 1-0026 at 27:2-3], no reported data support this conclusion. Significantly, the statement in the study that there were no clinically significant changes in serum sodium (PK) and osmolality (PD) at any time point – including pre-infusion and 2, 4 and 6 hours post infusion – is not supported by any reported data. And the researchers' conclusion that the decreases in serum sodium and osmolality that were observed "were entirely attributable to the water-loading methodology required by the study design" cannot be tested because there was no placebo (control) group with which to compare the study group. [Vis Affidavit ¶¶ 61-63.]

FF180. Further, Example 8 reports data from a continuous i.v. infusion of desmopressin over two hours – an intradermal, not transmucosal, administration route with a bioavailability of 100% – which is not a form that a POSITA would use in treatment. [Trial Tr. 871:5-10].

FF181. These defects in Example 8 are of particular significance because Example 8 is the only example in the common specification that is not also found in Ferring's GB patent application.

FF182. From his perspective as an individual who regularly deals with extrapolating and interpreting pharmacokinetic and pharmacodynamic data to predict the effect of drugs, Ferring's expert Mr. Vis concluded that Example 8's predictive value was limited. [Vis Affidavit ¶ 65.] This is consistent with Dr. Fein's admission that the study could not provide any information about the pharmacokinetic/pharmacodynamic relationship of low doses and duration of action as stated in the protocol. [Trial Tr. 420:9-23.] I credit Mr. Vis's testimony.

FF183. Formulation science is an unpredictable art that requires experimentation to determine if a particular formulation will be effective to achieve a specific pharmacodynamic

effect (here, the durations of action claimed in the asserted claims of the '321 patent). The missing data in the specification introduces bias that distorts the results. [Vis Affidavit ¶¶ 50-51.]

FF184. A POSITA would not find Example 8 an inventive disclosure because it conducts no PK analysis by which to assess whether the particular pharmacodynamic phenomena observed were matched by the claimed plasma concentration ranges. It is undisputed that the patent *says* that both PK and PD were analyzed in Example 8, but the CNF report underlying the data plainly states that neither the duration of action nor PK analyses were performed.

FF185. Further, none of the plasma concentrations recited in the Examples in the common specification falls within the plasma concentration ranges claimed in the patents-in-suit. Examples 4 through 6 were tested in Example 7, but the mean pharmacokinetic values obtained for those examples were well outside the limitations of the claim. That study used 200, 400, and 800 µg dosage strengths, with mean C_{maxes} of 14.25, 30.21, and 65.25 pg/ml respectively. The specification reports only *mean* PK values in this range, it does not give individual data showing the variability of the C_{max} values, nor does it report the standard deviation or coefficient of variation for these mean values. [JX-1-0022 at 20:2-4; Trial Tr. 51:8-14.] Owing to the linearity of desmopressin at these doses, one might expect that administering a lower dose of the sublingual ODT could achieve a C_{max} under 10 pg/mL, but the common specification does not include an example testing doses of the sublingual ODT lower than provided in Example 7.

FF186. The common specification also does not correlate the plasma concentrations claimed in the asserted claims with the desired antidiuretic effect. [Spaans Invalidity Affidavit ¶¶ 107-108; Trial Tr. 1068:17-1069:7.]

FF187. Because there is no single working example in the common specification that provides both the pharmacokinetic and pharmacodynamic data for a particular formulation, the

predictive value of the data in the common specification is severely limited. In order for the data in the common specification to have predictive value that allows extrapolation to other formulations and routes of administration, the common specification would need to disclose individual plasma concentration and individual pharmacodynamic response data. The individual pharmacokinetic data may allow one to create a model of the plasma concentration over time curves and use that model to predict the plasma concentrations over time for other formulations. Similarly, the individual pharmacokinetic and pharmacodynamic data allow for modeling of each individual concentration effect curve and allow the information to be aggregated to help build a predictive model, which potentially could then be used to provide an individual estimate of the duration of action when using a different formulation (e.g., a different dosage form or administration route) or a different study population (e.g., patients rather than healthy volunteers). [Vis Affidavit ¶ 66.]

FF188. The data in the common specification are therefore insufficient to allow a POSITA to model the plasma concentration over time curves (i.e., the pharmacokinetic effect) or the antidiuretic effect (i.e., the pharmacodynamic effect) as a function of desmopressin blood plasma concentration. Without these data, which are missing from the common specification, it is not possible to extrapolate how another dosage form would work or to extrapolate how any specific individual (much less a patient rather than a healthy volunteer) in another population would react. [Spaans Invalidity Affidavit ¶¶ 91-96; Trial Tr. 1062:8-1064:16; Vis Affidavit ¶ 66; Trial Tr. 653:12-655:1.]

J. Recent Commercialization of Desmopressin and the Patents-in-Suit

FF189. Both parties have offered a low dose desmopressin product for the treatment of nocturia in the United States.

FF190. On or before June 22, 2009, Ferring filed New Drug Application ("NDA") No. 022517, pursuant to 21 U.S.C. § 355(b), seeking approval to engage in the commercial manufacture, use or sale of a product to be known as NOCDURNA (desmopressin acetate) sublingual tablets for the treatment of nocturia in the United States. [PX-11.]

FF191. On June 21, 2018, the FDA approved Ferring's NDA. [PX-13.]

FF192. Ferring launched NOCDURNA on November 8, 2019. [PX-48.] It has been sold continuously since that date. [PX 14 at FERSER0381392-94.]

FF193. On February 4, 2016, Serenity filed an NDA seeking approval to engage in the commercial manufacture, use or sale of a product to be known as NOCTIVA (desmopressin acetate) nasal spray for the treatment of nocturia. [PX-10.]

FF194. On March 3, 2017, the FDA approved Serenity's NDA. [Fein Affidavit ¶ 70.]

FF195. Avadel, the commercial partner of Serenity and Reprise, failed to successfully market NOCTIVA and has filed for bankruptcy. As a result, NOCTIVA is no longer sold commercially. [*Id.* ¶ 77.]

K. The Parties' Litigation History

FF196. The parties have been litigating over their various patents, both here and in Europe, continuously for virtually a decade.

1. The European Action

FF197. Currently, there is a proceeding in the Hague involving EP168419 ("EP 419") – the European counterpart of the patents-in-suit.

FF198. EP 419 is not yet granted. After the EPO issued a communication in February 2011 indicating that it intended to grant the patent, Ferring initiated a proceeding claiming inventorship in and ownership of EP 410.

FF199. Specifically, Ferring brought several claims seeking, *inter alia*: a declaration in law that Dr. Nørgaard is the inventor of the subject of EP 419 and related applications; and a declaration in law that Dr. Fein is not the inventor of the subject of EP 419 and related applications. [D.I. 698, Ex. 1, ¶ 4.1.]

FF200. On March 12, 2014, a three-judge panel in the District Court of the Hague dismissed the claims. [D.I. 698, Ex. A, ¶ 3.] Ferring appealed the decision. Dutch appeal proceedings are entirely *de novo* in the sense that the entire case is tried anew without the exclusion of new evidence and new arguments. Ferring alleges that relevant documents became available from discovery in the U.S. proceedings only after the First Instance Decision was rendered. [D.I. 295 ¶¶ 17-20.]

FF201. On February 25, 2020, the Hague Court held a hearing in which it granted Ferring's request to introduce materials concerning the 2012 Action, including Judge Castel's decision regarding the July 2019 trial into the record for the appeal. [D.I. 698, Ex. A, ¶¶ 12-13.]

FF202. The EPO halted the prosecution of EP 419, and under the EPO's rule, EP 419 will not proceed to grant the patent as long as such entitlement proceedings are kept pending before a national court. [D.I. 698, Ex. A, ¶ 2.]

2. The 2012 Action

FF203. In 2012, Ferring brought an action under 35 U.S.C. § 256 to correct inventorship of the same patents-in-suit at issue in this litigation ("the 2012 Action"). Ferring alleged that the patents improperly named Seymour Fein as the sole inventor of the '203, '321, and '761 patents and that the true inventors were Jens Peter Nørgaard and Thomas Senderovitz. [2012 Action, D.I. 1.]

FF204. My predecessor in this case, The Hon. Robert Sweet, issued an order on September 22, 2015, in which he concluded that Ferring should be equitably estopped from pursuing § 256 correction of inventorship claims with respect to the Fein patents. [2012 Action, D.I. 190.] Ferring is appealing that decision to the Federal Circuit. [*Ferring v. Allergan*, Appeal No. 2020-1098 (Fed. Cir.)][11]

FF205. Two years after Ferring initiated the 2012 Action, in 2014, Serenity, Reprise, and Allergan counterclaimed with their own § 256 cause of action directed to two of Ferring's patents – U.S. Patent No. 7,569,429 and U.S. Patent No. 7,947,654 (collectively, the "Ferring patents") – claiming that Dr. Fein was the sole inventor or, alternatively, a co-inventor. [2012 Action, D.I. 93.]

FF206. Judge Sweet also dismissed Allergan, Serenity, and Reprise's claims that Dr. Fein was the sole inventor of Ferring's '429 and '654 patents. [2012 Action, D.I. 212.]

FF207. The trial of Serenity/Reprise/Allergan's counterclaims (shorn of Allergan) began before Judge Sweet on February 21, 2018; was interrupted and resumed (essentially, started over) before my colleague, The Hon. P. Kevin Castel, in June 2019. The action went to trial on the issue of whether Dr. Fein should be added as a co-inventor to the Ferring patents, wherein Serenity and Reprise alleged that Dr. Fein had contributed to the "sublingual administration" and "low dose" aspects of certain claims. [*See* 2012 Action, D.I. 453 ¶¶ 6, 10.] On September 27, 2019, the Judge Castel ruled, that "Serenity and Reprise have not proven by clear and convincing

[11] This particular ruling was made in a lawsuit not before this court, and I will as a result refrain from opining whether, in light of the full record now before me, I would agree with it. I will note that I would likely make a much more limited ruling today about the collateral estoppel effects of Judge Sweet's equitable estoppel ruling than I did before I was fully familiar with the record. However, as we tried the case on the basis of the ruling I made last summer – and since any amendation to that ruling would make no practical difference to the result reached after trial – I merely make note of this fact.

evidence that [Dr.] Fein contributed 'to the conception of the subject matter' of claims of the patents-in-suit in any matter that was not insignificant in quantity." [2012 Action, D.I. 453 ¶ 142.]

3. This Action

FF208. Ferring brought this declaratory judgment action in April 2017 against Serenity, Reprise, and Allergan seeking freedom to operate with respect to Ferring's NOCDURNA product based on the United States Food and Drug Administration's ("FDA") imminent approval of Ferring's New Drug Application for NOCDURNA. [D.I. 1, *as amended by* D.I. 18.][12]

FF209. In response to the amended complaint, on July 14, 2017, Serenity and Reprise filed a motion to dismiss claiming that "Ferring's product [NOCDURNA] will never be approved, much less approved any time soon." [D.I. 25; D.I. 78 at 4:2-5.]

FF210. In September 2017, Serenity and Reprise then found a new business partner, Avadel Specialty Pharmaceuticals, LLC ("Avadel") to commercialize NOCTIVA.

FF211. In May 2018, Serenity and Reprise filed a Citizens Petition with the FDA seeking to block the approval of NOCDURNA. Avadel also filed its own Citizen Petition attempting to block approval of NOCDURNA.

FF212. Despite Serenity, Reprise, and Avadel's attempts to block approval of NOCDURNA, on June 21, 2018, the FDA approved Ferring's NDA No. 022517. [PX-13 at FERSER0367487.]

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[12] In the original complaint, there were three patents-in-suit—the '203 patent, the '321 patent, and U.S. Patent No. 7,799,761 ("the '761 patent"). The '761 patent was dismissed from this action by the court in May 2019 on Serenity, Reprise, and Avadel's representation that they "have never alleged, and will never allege that Ferring's NOCDURNA product infringes the '761 patent." [D.I. 495.]

FF213. Upon FDA approval of NOCDURNA, Serenity and Reprise, along with Avadel, promptly counterclaimed for infringement of the patents in suit [D.I. 101] and filed a motion for a preliminary injunction seeking to block Ferring from selling NOCDURNA in the United States. [D.I. 117.] The court held a six-day hearing on the motion in October 2018 and, on November 8, 2018, the court denied Counterclaimants' request for a preliminary injunction. [D.I. 300.] The following day – November 9, 2018 – Ferring launched NOCDURNA in the United States.

FF214. NOCTIVA was launched in May 2018, approximately six months prior to NOCDURNA's launch. NOCTIVA's failed commercialization, in part, caused Avadel to file for bankruptcy on February 6, 2018.

FF215. As part of the bankruptcy, the NDA for NOCTIVA (which was owned by Avadel) was sold to a third party, Roivant, while the patent rights remained with Serenity and Reprise. As a result, NOCTIVA is no longer on the market because Serenity and Reprise no longer have a commercial partner to sell NOCTIVA and Roivant exclusively holds the NDA to sell NOCTIVA in the United States. Avadel is no longer involved in this action.

L. The Asserted Claims of the Patents-in-Suit

FF216. The patents-in-suit are generally directed to the use of the drug desmopressin to treat various diseases or conditions, including incontinence, nocturia, primary nocturnal enuresis ("PNE"), or for inducing voiding postponement in general.

FF217. U.S. Patent No. 7,405,203 (the "'203 patent") is titled "Pharmaceutical Compositions Including Low Dosages of Desmopressin." It lists Dr. Fein as the sole inventor and Reprise as the assignee. [JX-1.]

FF218. U.S. Patent No. 7,579,321 (the "'321 patent") is titled "Pharmaceutical Compositions Including Low Dosages of Desmopressin." It lists Dr. Fein as the sole inventor and Reprise as the assignee. The '321 patent is a continuation of the '203 patent. [JX-2.]

FF219. The '203 patent and the '321 patent are known herein as the patents-in-suit.

FF220. The patents-in-suit are listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* ("Orange Book") as covering Counterclaimants' drug NOCTIVA , which is the subject of NDA No. 201656. [PX-10.]

FF221. The issues for decision after trial are whether the patents-in-suit are valid, and, if they are, whether Ferring's product NOCDURNA – an FDA-approved orodispersible low dose formulation of desmopressin marketed for the treatment of the voiding disorder nocturia – infringes on the asserted claims of the patents-in-suit.

FF222. Counterclaimants assert claims 6, 10, 11, 12, and 13 of the '203 patent.

FF223. Claim 6 is a dependent claim that depends from claim 1. Claim 1 reads:

> A method of treating nocturia, primary nocturnal enuresis, or incontinence, or for inducing voiding postponement, said method comprising administering to a patient in need thereof a pharmaceutical composition comprising a dose of desmopressin sufficient to achieve a maximum desmopressin plasma/serum concentration no greater than 10 pg/ml and maintaining the concentration within the range of about 0.5 pg/ml for about four to six hours.

Claim 6 reads:

> The method of claim 1, comprising administering said composition by transmucosal delivery.

FF224. Claim 10 is an independent claim. It reads:

> A method for inducing an antidiuretic effect in a patient comprising the step of administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration no greater than 10 pg/ml.

FF225. Claim 11 is a dependent claim that depends from claim 10. It reads:

The method of claim 10, wherein said patient is suffering from incontinence, primary nocturnal enuresis (PNE), or nocturia.

FF226. Claim 12 is a dependent claim that depends from claim 10. It reads:

The method of claim 10, wherein said desmopressin pharmaceutical composition is administered in an amount and for a time sufficient to establish a serum/plasma desmopressin concentration no greater than about 5 pg/ml.

FF227. Claim 13 is an independent claim. It reads:

A method for treating a patient suffering from nocturia comprising administering to a patient a pharmaceutical composition comprising desmopressin by transmucosal, transdermal, or intradermal delivery in an amount and for a time sufficient to establish a maximum serum/plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml.

FF228. Counterclaimants also assert claims 3, 5, 6, 7, and 12 of the '321 patent.

FF229. Claim 3 is a dependent claim that depends from claim 1. Claim 1 reads:

A method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg by intranasal, transdermal, intradermal, transmucosal, or conjunctival administration, said amount being therapeutically effective to produce an antidiuretic effect lasting for no more than between about 4 and about 6 hours.

Claim 3 reads:

The method of claim 1 further comprising advising a patient that fluid intake should be restricted after administration.

FF230. Claim 5 is a dependent claim that depends from claim 1. It reads:

The method of claim 1 comprising administering desmopressin to a patient suffering from nocturia, primary nocturnal enuresis (PNE), or incontinence.

FF231. Claim 6 is a dependent claim that depends from claim 1. It reads:

The method of claim 1 wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 10 pg/ml.

FF232. Claim 7 is a dependent claim that depends from claim 1. It reads:

The method of claim 1 wherein the method produces a plasma/serum desmopressin concentration in the patient of a maximum of no more than about 5 pg/ml.

FF233. Claim 12 is a dependent claim that depends from either claim 1 or claim 8. Claim 8 reads:

> A method for inducing voiding postponement comprising administering to a patient an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg for less than about 5 hours after administration.

Claim 12 reads:

> The method of claim 1 or 8 comprising administering the desmopressin by transmucosal administration.

M. The Court's Claim Construction

FF234. The Court, in the person of the late Judge Robert Sweet, issued its Opinion and Order on claim construction on January 22, 2019. [D.I. 421.] [Stipulated Fact 27.] That decision, including the stipulated meanings therein, is deemed incorporated into these findings of fact. [D.I. 421 at 8.]

FF235. The Court construed the preamble of claims 1 and 19 of the '321 patent ("a method for inducing voiding postponement in a patient while reducing the risk that the patient develops hyponatremia comprising") "consistent with its plain and ordinary meaning as a statement of purpose—dual purposes, really" and "requires no further construction." [D.I. 421 at 13-14.]

FF236. The Court construed "transmucosal," appearing in claims 2, 6, 10, and 13 of the '203 patent and in claims 1, 12, and 19 of the '321 patent, as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." [D.I. 421 at 17.]

FF237. The Court construed "transmucosal delivery" or "transmucosal . . . delivery," appearing in claims 2, 6, 10 and 13 of the '203 patent as "delivering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." [D.I. 421 at 19.]

FF238. The Court construed "delivering to the bloodstream . . . by [via] transmucosal . . . administration," appearing in claims 1 and 19 of the '321 patent, as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." [D.I. 421 at 21.]

FF239. The Court construed "transmucosal administration" or "administering . . . by transmucosal administration," appearing in claim 12 of the '321 patent, as "administering desmopressin by way of a mucosal tissue, such as the sublingual mucosa." [D.I. 421 at 21.]

FF240. The Court stated that the term "a dose of desmopressin sufficient to achieve a maximum desmopressin plasma/ serum concentration no greater than 10 pg/ml," appearing in claim 1 of the '203 patent, "has a well-understood meaning to a person of ordinary skill in the art. It requires no construction." [D.I. 421 at 31.]

FF241. The Court stated that the term "desmopressin . . . in an amount . . . sufficient to establish a maximum serum/ plasma desmopressin concentration no greater than 10 pg/ml," appearing in claim 10 of the '203 patent, "has a well-understood meaning to a person of ordinary skill in the art" and "the term requires no further construction." [D.I. 421 at 32.]

FF242. The Court stated that the term "desmopressin pharmaceutical composition . . . in an amount . . . sufficient to establish a serum/ plasma concentration no greater than about 5 pg/ml," appearing in claim 12 of the '203 patent, "has a meaning understood to a person of ordinary skill in the art and requires no further construction." [D.I. 421 at 33.]

FF243. The Court stated that the term "desmopressin . . . in an amount . . . sufficient to establish a maximum serum/ plasma desmopressin concentration greater than 0.1 pg/ml and less than 10 pg/ml," appearing in claim 13 of the '203 patent, "has a meaning understood to a person of ordinary skill in the art. It requires no further construction." [D.I. 421 at 33-34.]

FF244. The Court stated that the term "delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg . . . said amount being therapeutically effective to produce an antidiuretic effect," appearing in claim 1 of the '321 patent, requires no construction except that the claim term "about 2 ng/kg" is construed as "about 2 ng/kg based on the standard 70 kg human body weight estimate." [D.I. 421 at 38.]

FF245. The Court stated that the term "delivering to the bloodstream of the patient an amount of desmopressin no more than about 1 ng/kg," appearing in claim 2 of the '321 patent, "has a well-understood meaning to persons of ordinary skill in the art and requires no further construction" except that the claim term "about 1 ng/kg" is construed as "about 1 ng/kg based on the standard 70 kg human body weight estimate." [D.I. 421 at 38.]

FF246. The Court stated that the term "an amount of desmopressin sufficient to produce in the patient a urine osmolality ranging above about 300 mOsm/kg," appearing in claim 8 of the '321 patent, "has a well-understood meaning to a person of ordinary skill in the art" and "requires no further construction." [D.I. 421 at 39.]

FF247. The Court construed "about 2 ng/kg desmopressin," appearing in claims 1 and 17 of the '321 patent, as "about 2 ng/kg based on the standard 70 kg human body weight estimate." [D.I. 421 at 39.]

FF248. With respect to the "dose" limitations above, the Court stated that "Neither claim 1 of the 203 Patent, nor the other asserted claims, reference a numerical dose or dose range of desmopressin." [D.I. 421 at 23.] The Court further stated that the asserted claims do "not define a particular dose range—neither expressly nor by implication . . . ." [D.I. 421 at 28; *see also* D.I. 421 at 35 ("There is no dose limitation in claim 1 of the 321 Patent and the Court finds no express intent in the Common Specification to redefine its scope to include one.").]

FF249. Finally, the Court stated that Dr. Fein's removal of dose-specific language and the word "low" from the phrase "low dose" from his claims during prosecution indicated that he intended to claim more broadly. [D.I. 421 at 30.]

N. Findings of Fact Relating to Written Description and Enablement

FF250. The Examiner originally rejected the claims of the '203 patent as initially drafted on several grounds, including lack of written description and enablement. [JX-7-0181-98.] The rejection was based in part on the fact that the original claims were broad and generic in nature. The Examiner's October 17, 2007 non-final office action stated:

> It is unquestionable that the claims are broad and generic, with respect to all possible combinations encompassed by the claims. The possible structural variations are limitless to any desmopressin composition formulated for the various routes of administration. Although the claims may recite some functional characteristics, the claims lack written description because there is not disclosure of a correlation between function and structure of the compositions. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus, being void of any single example that functions as claimed, and the specification does not provide sufficient descriptive support for the myriad of compositions embraced by the claims.

[JX-7-0193-94.]

FF251. Dr. Fein then amended the claims and specification. [JX-7-1884-88.]

FF252. The Examiner withdrew the rejection. In the Notice of Allowability, issued on April 7, 2008, the Examiner stated the following with respect to written description and enablement:

> The specification discusses producing Cmax in a linear manner for doses p.o. of 200, 400 and 800 μg and discusses Cmax values for i.v. administration. Taken together with these examples, along with the discussion of the necessity for 'low dosages', one would reasonably find support under 112 1st paragraph for a Cmax no greater than 10 pg/ml.
>
> With regards to the enablement/written description requirements, the examiner finds the current amended claims are supported by the disclosure sufficient to withdraw the rejections. The claims are no longer drawn to treating any/all diseases,

> but rather to a select group of diseases with a single compound, and it would not pose an undue burden to determine what dosage/dosage form would be necessary to achieve the required desmopressin Cmax as in the claims, particularly since the examples show a linear correlation between dose and Cmax. Achieving the Cmax would amount to nothing more than routine optimization.

[JX-7-0315.]

FF253. The asserted claims of the patents in suit are all generic in nature, in that they are directed to methods treating different voiding disorders by administering to a patient an open-ended set of desmopressin formulations and doses that satisfy either the pharmacokinetic limitations (the asserted claims of the '203 patent and asserted claims 6 and 7 of the '321 patent) or the pharmacodynamic limitations (the asserted claims of the '321 patent). [JX-1-0026 cl. 6, 10, 11, 12, 13; JX-2-0027-28 cl. 3, 5, 6, 7, 12; Trial Tr. 19:21-24; 30:8-21:3; 310:17-311:7; Verbalis Affidavit ¶ 21.]

FF254. The pharmacokinetic limitations (i.e., the plasma concentrations) are functional limitations in that they describe the results that flow from a particular formulation, route of administration, and dose. [Trial Tr. 19:21-19:24.]

FF255. Similarly, the pharmacodynamic limitations of the asserted claims of the '321 patent (i.e., the antidiuretic durations of action) are functional limitations in that they describe the results that flow from a particular formulation, route of administration, and dose. [Trial Tr. 20:8-21:3.]

FF256. The common specification includes no examples that meet any of the functional limitations of the claims. The disclosures in the table in column 17 of allegedly effective daily dose ranges for various routes of administration are accompanied by no examples that teach or show that they are, in fact, effective to meet the functional limitations of the asserted claims or to provide therapeutic efficacy. Nor would a POSITA expect all formulations for each route of

administration that have desmopressin doses in the disclosed ranges to meet the functional limitations of the asserted claims. [DX-38-0041 at 11.14; Spaans Invalidity Affidavit ¶ 85; Trial Tr. 1034:12-1037:14, 1027:5-1028:7, 1064:2-1064:16, 1067:22-1068:5; Trial Tr. 1139:17-1139:21 (Mayersohn).]

FF257. Subject to the restrictions on the routes of administration in certain of the asserted claims, the asserted claims can encompass any desmopressin formulation and dose amount that meets the functional limitations of the claim. [Trial Tr. 1069:8-1069:11 (Spaans); Trial Tr. 1139:17-1139:21 (Mayersohn); Trial Tr. 311:2-311:7 (Fein).]

FF258. The common specification provides no guidance on any structural features of any given formulation or route of administration that would assist a POSITA in identifying the species that fall within the asserted generic claims. [Trial Tr. 1139:17-1140:16 (Mayersohn).]

FF259. Notwithstanding the above, Dr. Mayersohn testified, credibly, that the mean C_{max} of desmopressin was linear across doses of the sublingual orodispersible form set forth Example 7. As a result, he testified that a POSITA could project a mean C_{max} for the sublingual orodispersible form at different doses – even if those dosage levels were lower (or higher) than the levels tested in the various trials described above. To Dr. Mayersohn, this fact demonstrates that Dr. Fein had possession of the claimed method, and that the teachings of the specification would allow a POSITA to run routine experiments and "titrate up" at the patient level, thereby figuring out how to achieve both the claimed plasma concentration ranges and the claimed duration of action using a sublingual orodispersible dosage form set forth in Example 7. For this reason, he concluded that the written description and enablement requirements were met. [Mayersohn Rebuttal Affidavit ¶ 143.]

FF260. Dr. Mayersohn testified that, using Example 7, a POSITA would be able to find appropriate doses based on a simple proportionality equation. $Dose_2 = F_1/F_2 * Dose_1$, where F_1 and F_2 are different routes of administration.

FF261. However, a POSITA would know that Example 7's demonstration of mean C_{max} linearity is limited to the specific dosage form tested – i.e., an orodispersible sublingual tablet with excipients in the same ratios as those in Examples 4, 5, and 6. This would not necessarily translate to other dosage forms – even dosage forms that have the same qualitative composition but a different quantitative composition (i.e., the same excipients, but different amounts). [Spaans Invalidity Affidavit ¶ 94; Mayersohn Rebuttal Affidavit ¶¶ 82-83.]

FF262. Dr. Mayersohn's proposed proportionality equation elides the key distinctions between dosage form, dose, and administration route, and their effects on the PK/PD profile of the drug. The drug is more or less bioavailable depending on its route of administration. Administering desmopressin directly into the bloodstream (IV administration, as was done in CS009 and the CNF experiment that was derived from CS009) delivers 100% bioavailability. Ferring's 100 microgram oral tablets deliver the drug at anywhere between .08 and .16% bioavailability. [DX-33-0010.] Sublingual administration of an orodispersible tablet reports a range of bioavailability between 0.21% and 0.31%. [JX-5-0009.] The Examples in the patents-in-suit do not disclose what proportion of the bioavailability of the sublingual orodispersible form is due to the route of administration, or the particular excipients in the dosage form. In the absence of that, a POSITA is left without sufficient information to predict the relationship between administration route and PK parameters. Since it is impossible to calculate a dose that will be both safe and potentially effective for a particular route of administration without understanding the characteristics that determine its bioavailability, a POSITA would have to conduct testing to

determine bioavailabilities for the other claimed routes of administration. As will be seen below, that testing would be extensive.

FF263. Crucially, the asserted claims encompass far more than just the orodispersible sublingual tablet. Asserted claim 6 of the '203 patent and asserted claim 12 of the '321 patent limit their respective independent claims to transmucosal routes of administration, but transmucosal administration/delivery includes administering or delivering desmopressin to any mucosal tissue, including the mucosa in the mouth, the eyes, the gastrointestinal tract and the rectum. There are a minimum of seven ways to achieve transmucosal administration listed in the common specification – ODTs, wafers, film, effervescents, eyedrops, suppositories and enemas – and according to Dr. Mayersohn, there is an eighth way, swallowing an oral tablet. [JX-1-00026 cl. 6; JX-2-0028 at cl. 12; Trial Tr. 1152:21-1153:1; 1154:1-7.] The transmucosal formulations that are inserted in the mouth can be delivered buccally, sublingually, or supralingually. [JX-1-0021 at 17:1-15.]

FF264. Each of the other asserted claims includes all transmucosal routes of administration and other routes of administration – intravenous, subcutaneous, intranasal, conjunctival, transdermal and intradermal – most of which can be delivered in various formulations (bolus, infusion, depot, patch, gel, cream, ointment, iontophoretic). [JX-1-0020 at 16:51-64; Trial Tr. 1150:8-1150:12 (Mayersohn).]

FF265. Limiting the discussion to transmucosal administration: desmopressin can be formulated for delivery via each route with different types of excipients, which will affect the release and absorption characteristics of the desmopressin in the formulation – resulting in different plasma concentration curves and different durations of action. [DX-38-0044, 49; Spaans Invalidity Affidavit ¶ 87; Trial Tr. 1148:21-1148:22 (Mayersohn).]

FF266. Take for example the sublingual orodispersible tablet – the only method of transmucosal administration that is discussed in the common specification. Assuming that each formulation contains four constituent excipients besides desmopressin (the number of excipients in Examples 1 through 6) yields a total of twenty-four possible formulations. If each of the excipients in the above example can occur in one of five different amounts, there would be approximately 2,880 different combinations, just for the orodispersible tablet alone.

FF267. Assuming that transmucosal formulations only include oral tablets, orodispersible tablets, wafers, films, effervescent formulations, eye drops, sublingual formulations, supralingual formulations, buccal formulations, suppositories, and enemas – and that each different type of formulation also has four excipients that can occur in five different amounts – there are approximately 31,680 different formulations that would fall within the scope of the asserted claim 6 of the '203 patent and asserted claim 12 of the '321 patent if they met the claimed functional limitations.

FF268. Accordingly, even the asserted claims that claim only the transmucosal route of administration still cover an open-ended set of desmopressin formulations that can be used to treat in accordance with the claimed methods. The ability to produce an effect within the claimed methods depends entirely on whether the particular formulation meets the claimed functional limitations. Indeed, the asserted claims even cover any later developed desmopressin formulations that meet the functional limitations. [Trial Tr. 1155:6-1163:12 (Mayersohn)].

FF269. As noted above, the asserted claims other than asserted claim 6 of the '203 patent and asserted claim 12 of the '321 patent, include routes of administration in addition to the transmucosal route of administration, such as intravenous (bolus, infusion), intranasal, intradermal (bolus, infusion, depot), transdermal (passive via patch, gel, cream, ointment or

iontophoretic), and subcutaneous (bolus, infusion, depot). [Trial Tr. 1140:17-25; JX-1-0020 at 16:51-64.] Each new route of administration, and each new form in which the drug can be administered via that route, increases the number of formulations that might potentially achieve the patent's claimed functional limitations.

FF270. The common specification provides no teaching or disclosure of how any route of administration other than sublingual will result in low plasma concentrations, have therapeutic efficacy, or reduce the risk of hyponatremia. [Trial Tr. 1139:17-1140:25(Mayersohn).]

FF271. The common specification does not disclose any working examples of formulations that meet the pharmacokinetic parameters of the asserted claims.

FF272. The common specification does not disclose any working examples of claimed formulations that meet the pharmacodynamic limitations of the asserted claims. [Spaans Invalidity Affidavit ¶¶ 85-97; Vis Affidavit ¶¶ 43-57.]

FF273. In order to determine if a particular formulation, administered via a specific route, would meet the functional limitations of the asserted claims, a POSITA would need to conduct a clinical trial. Based on the results of the clinical trial, if the tested formulation did not meet the claim limitations, a POSITA would need to modify the formulation and then conduct additional clinical trials to determine if the new formulation met the functional limitations of the asserted claims. [Trial Tr. 425:9-426:3 (Fein); Spaans Invalidity Affidavit ¶ 96; Mayersohn Rebuttal Affidavit ¶ 144; *see, e.g.*, DX-82.]

FF274. In order to determine an appropriate dose for a particular dosage form with a particular formulation and a particular route of administration, it is necessary to know the bioavailability of the specific dosage form, as formulated. The bioavailability can be affected by many variables, including the excipients used, the relative amounts of the excipients to each

other and to the drug, and the method of manufacture. [DX-73 (FDA Noctiva Warning), Trial Tr. 196:13-197:11; 233:15-233:25.]

FF275. Even relatively small changes in the formulation can affect the bioavailability. [Spaans Invalidity Affidavit ¶ 96; Mayersohn Rebuttal Affidavit ¶¶ 82-85; DX-73 (FDA NOCTIVA Warning), Trial Tr. 196:13-197:11, 1186:7-1186:12.]

FF276. Illustrative of the unpredictability of desmopressin formulations is that the FDA later required black box labels on NOCTIVA to warn patients about the possibility that they might experience hyponatremia – the possibility of which the patents-in-suit claim to reduce – notwithstanding the purportedly low dose that is a feature of the product because: "Two sprays of Noctiva .83 micrograms are not interchangeable with one spray of Noctiva 1.66 micrograms." The FDA's "concern [was] that two separate sprays of .75 micrograms could potentially increase desmopressin exposures beyond that achieved with one spray, which could increase the risk of hyponatremia . . . because the two sprays of .75 micrograms contain twice as much penetration enhancer than one spray of 1.5 micrograms. Also, in a pharmacokinetic study, a 1 mcg dose given as one .5 mcg spray in each nostril led to about a two-fold higher systemic exposure compared to two sprays of 0.5 mcg in one nostril." [Trial Tr. 195:23-197:11; DX-73-0007.] In other words, while the dose of desmopressin administered would be the same – proceeding in a "linear" fashion – different configurations of excipients, and even different configurations of administration, have dramatic effects on the pharmacokinetic and pharmacodynamic character of the form.

FF277. The only way to determine the bioavailability of a particular dosage form with a particular formulation for a particular route of administration is to test the dosage form in a human clinical trial. Therefore, for each new dosage form it would be necessary to conduct a

clinical trial to determine the bioavailability and thus the resulting plasma concentrations. [Trial Tr. 1184:15-1185:1; 1186:7-1186:12 (Mayersohn).] Those clinical trials would be voluminous and neither trivial nor predictable. [Spaans Invalidity Affidavit ¶ 96.]

FF278. The only evidence introduced at the trial about the bioavailability of desmopressin concerned its delivery via intravenous administration, Ferring's oral tablet and an orodispersible tablet. There is no evidence that anyone – and certainly not Dr. Fein – has ever analyzed the bioavailability of desmopressin when delivered via any of the other myriad forms of transmucosal administration, or via intranasal, intradermal, transdermal, and subcutaneous routes of administration (all of which are specifically claimed in certain of the asserted claims). A POSITA would have to conduct a clinical study, like Ferring's CS004 (from which Example 7 is derived) or Comparative Example 4, in order to determine the relative bioavailabilities of the various routes of administration and other dosage forms. [Mayersohn Rebuttal Affidavit ¶ 144.]

FF279. Ferring has thus established by clear and convincing evidence that the program of experimentation needed to enable the invention across all the claims would be extensive. [Trial Tr. 1160:20-1163:12.]

O. The asserted claims are invalid for lack of enablement based on Dr. Fein's admissions in front of the EPO

FF280. Beyond the patents-in-suit, Dr. Fein filed additional patent applications directed to desmopressin. For example, Dr. Fein applied for patents in the United States Patent and Trademark Office ("PTO") and European Patent Office ("EPO") directed to a particular nasal spray formulation. From those applications, the PTO issued U.S. Patent No. 9,539,302 (the "'302 patent") and the EPO issued European Patent No. 2442821 [DX-34] (the "Eur '821 patent"), both of which list Dr. Fein as the sole inventor.

FF281. The Eur '821 patent is a foreign counterpart of the '302 patent and has a single claim, which is directed to a "composition of matter comprising an intranasal desmopressin dose in the form of a plume ejected over a time interval from the nozzle of a metered dose spray device." [DX-34-0016 at cl. 1.]

FF282. The Eur '821 patent was subject to an opposition proceeding at the EPO. One of the prior art references cited in the opposition proceeding was the '203 patent, where it was referred to as "D8." [*See* DX-37-0018 ¶ 61.]

FF283. On August 7, 2018, Dr. Fein's representatives in Europe submitted to the EPO on behalf of Serenity a Response to the Notice of Opposition [DX-38] ("Opp'n Response").

FF284. The Opp'n Response also refers to the '203 patent as "D8." [DX-38.]

FF285. The Opp'n Response includes the statement:

> D8 is concerned with the problem of improving existing desmopressin formulations in general (without providing specific details), so that they are easy to use for patients and have less side effects (e.g. hyponatremia) (See Col. 2, lines 6-22). D8 further mentions that it would be desirable to have lower dosage of desmopressin for treatment of condition such as nocturia (col. 16, lines 25-45).

[DX-38-0043 ¶ 11.10.]

FF286. The Opp'n Response also states that:

> [T]he skilled person understands that D8's teaching is centered on sublingual dosage forms. D8 does not explore how to improve formulation nor findings [sic] ways of administering low dose of desmopressin for an intranasal dosage form, which results in low blood concentrations (no more than 15 pg/ml, preferably less than 10 pg/ml), while reducing variability, increasing bioavailability, having therapeutic efficacy (inducing an antidiuretic effects), and reducing the risk of hyponatremia.

[DX-38-0043 ¶ 11.12.]

FF287. The Opp'n Response further states:

> With respect to "low dose" desmopressin, D8 teaches the following: The dosages for the sublingual dosage form range between 0.5 ng to 20 mcg, and are said to be

> effective in establishing a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picogram desmopressin per mL plasma/serum (Col. 2, lines 26-37). D8 further teaches preferred (narrower) dosages in col. 4, lines 1-19, including of 0.5 or 1 mcg to 1 mg or 2 mcg to 800 mcg or 10 mcg to 600 mcg per or 0.5 ng to 20 000 ng or 0.05 mcg to 10 mcg or 0.1 mcg to 2 mcg. It is noteworthy that the broader (0.5 ng to 20 mcg) and narrower dosage ranges disclosed in col. 4, lines 1-19 (e.g. 0.1 mcg to 2 mcg) are specific to the sublingual dosage forms and do not apply to intranasal dosage forms.

[DX-38-0043 ¶ 11.13 (emphasis omitted).]

FF288. In addition, Opp'n Response states:

> It is noteworthy that the teaching of D8 with respect to the Table in Col. 17 is <u>not enabled</u>, i.e., there is [sic] no examples demonstrating that any of the suggested dose ranges are effective to establish a steady plasma/serum desmopressin concentration in the range of from about 0.1 picograms desmopressin per mL plasma/serum to about 10.0 picogram desmopressin per mL plasma/serum in a patient, let alone provide therapeutic efficacy for the conditions indicated above (e.g., inducing an antidiuretic effect for less than about 6 hours, and which lower the risk of hyponatremia).

[DX-38 at 44 ¶ 11.14 (emphasis in original).]

FF289. The Opp'n Response also states:

> [T]he skilled person would still need to refine (narrow) the broad dose range taught in D8 (0.1 mcg to 20 mcg) to arrive at the dose range of claim 1 (1-5 mcg or 0.75 mcg), and *perform tests to find dosage(s) that are effective* in producing blood levels of not more than 15 ± 3 pg/ml, preferably no more than 10 pg/ml, and show therapeutic efficacy (inducing an antidiuretic effect of about less than 6 hrs), and lead to a lower risk of hyponatremia. *This would amount to a research program.*

[DX-38 at 49 ¶ 11.37 (emphasis added).]

P. Findings of Fact Relevant to Inventorship

FF290. In the early 1990s, Dr. Fein – who is a board-certified internist and medical oncologist – claims to have formed a hypothesis that desmopressin "must be a more potent hormone than was previously thought and must exert an antidiuretic effect down to a much lower blood level than was previously thought, as low as one picogram per milliliter of plasma or lower." [Fein Affidavit ¶ 16.]

FF291. This hypothesis stemmed from his "experience with and knowledge of desmopressin" and his ideas about "what was causing the incidence of hyponatremia observed in the literature about desmopressin." [*Id.* ¶ 15.]

FF292. Prior to 2003, Dr. Fein did not publish, nor reduce to writing any of his ideas about desmopressin being a more potent drug than was known in the literature. There are no notes and no written records of any sort that memorialize Dr. Fein's purported thoughts, or that so much as suggest that he was thinking about desmopressin in the early 1990s. Dr. Fein is not a urologist or someone who would be expected to treat the types of voiding disorders that are the subject of the patents-in-suit.

FF293. Dr. Fein's invention as claimed in the patents-in-suit is far broader than his purported invention. Certain claims are independent of route of administration, while other claims recite:

- "administering said composition by *transmucosal*, *transdermal*, or *intradermal* delivery" [JX-1-0026 at cl. 2 (emphasis added)];
- "administering said composition by" a particular route of delivery: *intravenous*, *subcutaneous*, *transmucosal*, *transdermal*, and *intradermal*, respectively [JX-1-0026 at cl. 4-8 (emphasis added)];
- "administering to a patient a pharmaceutical composition comprising desmopressin by *transmucosal*, *transdermal*, or *intradermal* delivery" [JX-1-0026 at cl. 10 (emphasis added)];
- "administering to a patient a pharmaceutical composition comprising desmopressin by *transmucosal*, *transdermal*, or *intradermal* delivery" [JX-1-0026 at cl. 13 (emphasis added)];
- "delivering to the bloodstream of the patient an amount of desmopressin no more than about 2 ng/kg by *intranasal*, *transdermal*, *intradermal*, *transmucosal*, or *conjunctival* administration" [JX-2-0027 at cl. 1 (emphasis added)];

- "administering the desmopressin by" a particular route of delivery: *intranasal*, *transdermal*, *intradermal*, *transmucosal*, and *conjunctival*, respectively [JX-2-0027 to JX-2-0028 at cl. 9-13 (emphasis added)];

- "delivering to the bloodstream of the patient via *transdermal*, *intradermal*, *transmucosal*, or *conjunctival* administration" [JX-2-0028 at cl. 19 (emphasis added)]; and

- "delivering to the bloodstream of the patient via *intranasal* administration" [JX-2-0028 at cl. 20 (emphasis added)].

FF294. There is no evidence that Dr. Fein conceived of the "low dose invention" he claimed in the patents-in-suit. Instead, Dr. Fein's alleged "low dose invention" as claimed in the patents-in-suit was merely a hypothesis, one that had occurred to others – including scientists at Ferring – and on which those others had worked extensively before Dr. Fein had anything to do with desmopressin.

FF295. Ferring recognized that Dr. Fein did make some contribution to the invention for which it sought patent protection in Great Britain by virtue of his advocacy for delivering the drug sublingually rather than supralingually. It did so by listing Dr. Fein as one of the many inventors on its GB patent application, which predates all other patent applications in this case. However, Dr. Fein is one of six inventors listed on PCT '036 -- including Dr. Nardi, who Dr. Fein himself identified as co-inventor of the sublingual concept. [FF ¶¶ 79-101; 122-24.]

Q. The relevant time frame for conception

FF296. Dr. Fein's first alleged disclosure to Dr. Nardi of his alleged "inventive concepts" occurred in August 2001, in an oral conversation of which there are no notes; it was not accompanied by any written presentation. [Trial Tr. 320:22-321:16.]

FF297. The relevant time points for conception are (i) what occurred before Dr. Fein's oral conversation with Dr. Nardi in August 2001; (ii) the filing of Ferring's GB application on

May 6, 2002; (iii) the filing of Dr. Fein's PCT '463 application on May 7, 2003; and (iv) the filing of Dr. Fein's '100 application on November 12, 2003.

CONCLUSIONS OF LAW

I. Legal Standards and Principles Governing the Patents-in-Suit and their Examination

CL1. The patents at issue are subject to the pre-American Invents Act standards, including those found in Chapter 35 of the United States Code, Chapter 37 of the Code of Federal Regulation ("CFR"), and the MANUAL OF PATENT EXAMINING PROCEDURE, 8th ed. ("MPEP"). *See* MPEP § 2159.01; *see also, In re Portola Packaging, Inc.*, 110 F.3d 786, 788 (Fed. Cir. 1997) (stating that the MPEP "does not have the force of law, [but] provides guidance and instructions to examiners").

CL1. The courts "presume[] that the Patent Office complies with its own [procedural] rules, a presumption overcome only upon presentation of contrary evidence." *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, 346 F.3d 1094, 1103 (Fed. Cir. 2003); *see also In re NTP, Inc.*, 654 F.3d 1268, 1279 (Fed. Cir. 2011) ("As Congress acknowledged, examiners have limited time to review each application and cannot be expected to fully address every possible issue before them") (*citing* H.R. Rep. 107-120 (June 28, 2001)).

CL2. The presumption of validity under 35 U.S.C. § 282 is a rebuttable presumption. *See, e.g., Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1352 (Fed. Cir. 2013); *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259–61 (Fed. Cir. 2012) (vacating and remanding to the district court based on patent challenger raising a "substantial question of validity"); *see also Cleveland Clinic Found. v. True Health Diagnostics LLC*, 760 F. App'x 1013, 1021 (Fed. Cir. 2019) (noting that "deference" "to the examiner's decision to allow the

asserted claims" "is incorporated into the presumption of patent validity," and affirming the district court's dismissal of infringement claims by finding asserted claims invalid).

CL3. In the context of 35 U.S.C. § 112, "Any deference due to a Patent Examiner" may be overcome by "clear and convincing evidence that the specification does not support the asserted claims" of the patents in suit. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1329 (Fed. Cir. 2000); *see also In re NTP, Inc.*, 654 F.3d at 1279 (Fed. Cir. 2011) (finding that the examiner did not consider whether a continuation patent's specification complied with § 112).

II. The Asserted Claims Are Invalid for Lack of Written Description under 35 U.S.C. § 112, ¶ 1.

A. Applicable Legal Standards

"The specification shall contain a written description of the invention." 35 U.S.C. § 112, ¶ 1.

The written description requirement "plays a vital role in curtailing claims . . . that have not been invented, and thus cannot be described." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (citing *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010)).

As such, the "purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed. Cir. 2004) (internal quotation omitted).

Compliance with the written description requirement is a "fact-based inquiry" that necessarily varies "depending on the nature of the invention claimed." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 (Fed. Cir. 2002) (citation omitted).

Pursuant to the written description requirement, the applicant must "convey with reasonable clarity to those skilled in the art, as of the filing date sought, he or she was in possession of the invention. The invention is, for the purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (emphasis omitted).

Assessing "possession as shown in the disclosure requires an objective inquiry into the four corners of the specification." *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (citation omitted); *see also Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1161 (Fed. Cir. 2019) ("a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and *demonstrate that by disclosure in the specification of the patent*" (emphasis added; internal quotation omitted)).

"The written description requirement often becomes an issue in cases in which a broad genus is claimed and the specification discloses only one or a few species of that genus." *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 618 (D. Del. 2018), *aff'd on other grounds*, *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019).

The problem presented by generic claims "is especially acute with genus claims that use functional language to define the boundaries of the claimed genus." *Ariad*, 598 F.3d at 1349.

For such claims—genus claims that define the boundaries of the genus with functional language—to have adequate written description support, the specification must disclose "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize'

the members of the genus." *Id.* at 1350 (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)).

"A 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor*, 636 F.3d 1341, 1348 (Fed. Cir. 2011) (quoting *Regents*, 119 F.3d at 1566).

The written description requirement is "not a question of whether one skilled in the art *might* be able to construct the patentee's device from the teachings of the disclosure . . . . Rather, it is a question whether the application necessarily discloses that particular device." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008) (citing *Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987)).

For example, "[s]election of [a disease] from a list of diseases and selection of [a dosage] from a large range of possible dosages" involves "necessary picking and choosing to arrive at the claimed invention" and "does not indicate it was described." *FWP IP ApS v. Biogen MA., Inc.*, 749 F. App'x 969, 973 (Fed. Cir. 2018). Rather, Federal Circuit precedent "requires the specification itself to provide the blaze marks necessary to guide a skilled artisan to the claimed invention." *Id.*

By the same token, for claims directed to routes of administration of a drug, if little was known by the skilled artisan at the time of filing about administering the drug by those routes of administration or formulating the drug for administration by those means, and the specification reports only general information—e.g., that the methods comprise administering an "effective amount" by the claimed routes of administration, that the drug may be administered alone or in combination with other excipients, that dosages will be determined by the administering physician—the inventors' belief that scientists could practice the claimed invention is

insufficient to satisfy the written description requirement. *Wyeth v. Abbott Labs.*, 2012 WL 175023, at *9-10 (D.N.J. Jan. 19, 2012) (granting summary judgment of invalidity for insufficient written description and lack of enablement), *aff'd on other grounds*, 720 F.3d 1380 (Fed. Cir. 2013) (affirming invalidity for lack of enablement).

B. Conclusions of Law Relating to Written Description

1. The asserted claims are invalid for lack of written description under the standards set forth by Judge Bryson in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018).

CL4. The asserted claims are defined by functional limitations. [FF113-FF115.]

CL5. The asserted claims cover treatment with nearly any desmopressin formulation as long as the functional limitations of the claims are met. [FF117, FF121-FF125, FF132.]

CL6. Accordingly, the asserted claims are invalid for lack of written description because they inadequately describe the genus of formulations used in the claimed methods. [FF113-FF126.]

2. The asserted claims are invalid for lack of written description because there is no support for the claimed methods.

CL7. The common specification fails to disclose a specific dose or dose range that, when used in any dosage forms and routes of administration covered by the asserted claims, would achieve the claimed therapeutic effects and other recited properties (e.g., blood plasma concentrations) and, therefore, the common specification does not provide a practicing physician with enough information to recognize what is part of the invention. [FF188-FF189.]

CL8. The common specification fails to demonstrate that Dr. Fein was in possession of the methods for achieving the recited therapeutic effects for all of the dosage forms and routes of administration covered by the claims. The disclosure does not allow persons of ordinary skill in the art to recognize that Dr. Fein invented the claimed methods. [FF176, FF182.]

CL9. The asserted claims are invalid for lack of written description because there is inadequate support for the claimed methods of treatment. [FF176, FF182, FF188-FF189.]

3. The asserted claims of the '321 patent are invalid for lack of written description because there is no support for the claimed reduction of the risk of hyponatremia.

CL10. The common specification does not provide a sufficient disclosure regarding the claimed methods for reducing the risk of hyponatremia. Serum sodium data would be the minimum disclosure needed by a POSITA to evaluate whether there was a risk of hyponatremia. And even more would be needed to show that Dr. Fein actually invented—was in possession of—a method for reducing such a risk while still practicing the claimed methods (of achieving therapeutic efficacy via treating various voiding disorders, inducing voiding postponement, or inducing an antidiuretic effect), particularly with seemingly limitless combinations of dosage forms, routes of administration, and doses provided in the common specification. [FF179.]

CL11. Accordingly, the asserted claims of the '321 patent are invalid for lack of written description, because there is no support for the claimed reduction of the risk of hyponatremia. [FF183-FF189.]

C. Analysis

1. The asserted claims are broad and generic.

Ferring casts the asserted claims as broad and generic. They argue that the validity of the patents-in-suit should therefore be analyzed under the standards set forth in *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566 (D. Del. 2018). In that case, Judge Bryson of the Federal Circuit, sitting as a district judge in Delaware, invalidated a patent for insufficient written description where the specification contained "only a single embodiment within the broad scope of the claims." *Pernix*, 323 F. Supp. 3d at 626.

Serenity and Reprise argue that its claims are not generic and that *Pernix* is inapposite because the patents in suit "are directed to treating a select group of diseases with a single compound, desmopressin."

Serenity and Reprise are clearly wrong.

We begin with Dr. Fein's description of his invention. As he or others speaking for him have repeatedly said, including in testimony before Judge Castel at the Allergan trial, his ideas are limited in scope to (1) the sublingual administration of desmopressin (2) in a "low" dose that will achieve certain PK and PD parameters. At the trial in this action, Dr. Fein admitted that the claims in the patent-in-suit go beyond his "invention." [Trial Tr. 312:5-8; 373:2-15]. In a communication to the PTO, Dr. Fein further stated that he:

> [U]nderstood that many dosage forms could be devised by persons of skill in the art to achieve [a low dose range below about 10 pg/mL], and that it was *critical* to protect his invention to obtain a therapeutic method claim that was *unlimited with respect to the chemical or mechanical way the concentration profile is achieved.*
>
> [DX-35-0003 (emphasis added).]

Dr. Mayersohn, Serenity and Reprise's own expert, agreed. He testified that the claim language in the patents does not limit the desmopressin dosage forms, or route of administration, or the formulations that may be used, other than by the "limited number of body orifices available for administration of a drug." [Trial Tr. 1139:17-11:40:2.] He further testified that the claim does not provide any structural features of the formulation (like excipients used) or dosage form used (for example, a tablet or solution) [Trial Tr. 1140:10-16.]; and that the claims encompass any of the routes of administration and dosage forms set forth in the table found at column 17 of the common specification. [Trial. Tr. 1140:17-25.]

And the table at the top of column 17 in the '203 patent – a key disclosure for our purposes – includes an extraordinarily broad range of doses (from X to Y if administered in one

way, from A to B if administered in another, for each of six different routes of administration comprising 19 different specified methods of administration[13]). The specification posits that every dose within those ranges "can produce appropriate antidiuretic effect when administered by various routes. [JX-1-0021 at 17:1-15.] Additionally, the "Low Dosage Analysis and Applications" section of the common specification adds that pharmaceutical compositions may be administered by "any other method known in the art." [JX-1-0020 at 16:51-64.]

Even if we simply consider the transmucosal route of administration – which Dr. Fein testified is the "broadened version of the sublingual invention," [Trial Tr. 373:7-15; 1151:22-1152:12.], and which is the one route of administration encompassed by every one of the asserted claims – Column 17 in the '203 patent identifies seven different species of transmucosal dosage forms – orodispersible tablets, wafers, film and effervescent formulations, eyedrops, suppositories, and enemas. [Trial Tr. 1152:22-1153:1.] Dr. Mayersohn testified that an oral tablet (such as Ferring sold for many years) was also a transmucosal route of administration, because there are mucosa in the gut. [Trial Tr. 1154:1-4.] For just those eight transmucosal variations, considering variations in excipients used, there are thousands of possible formulations that are arguably encompassed by the claims. [Trial Tr. 1154:16-1157:10.] Each such variation impacts the bioavailability of the drug, and therefore the pharmacokinetic and pharmacodynamic effect of the final formulation. [Trial Tr. 1155:6-12.]

Given the range of options that purport to meet the functional limitations of the claim, it is obvious that the asserted claims belong to a remarkably broad genus. To use Dr. Fein's own

[13] (1) intravenous (bolus and infusion), (2) subcutaneous (bolus, infusion, depot), (3) intranasal, (4) transmucosal including buccal and sublingual (orodispersible tablets, wafers, film and effervescent formulations), conjunctival (eyedrops), rectal (suppository enema), (5) transdermal (passive via patch, gel, cream, ointment or iontophoretic, and (6) intradermal (bolus, infusion, depot). [JX-1-0021 at 17:1-15.]

words, the claims are "unlimited with respect to the chemical or mechanical way the concentration profile is achieved." [DX-35-0003.] While Serenity has at times argued that the claims are centered on "sublingual dosage forms" [DX 38-0043 at ¶11.12], the text of the claims is not "centered on" – and is certainly not limited to – sublingual dosage forms. The claims encompass all transmucosal dosage forms, and a great many other dosage forms as well."

Yet the specification, whose teachings are limited to one of the many claimed forms of transmucosal dosage – the sublingual orodispersible dosage form – is far narrower than the asserted claims.

It is, therefore, imperative that the patents-in-suit contain sufficient written description to establish that Dr. Fein was in possession, not just of his rather narrow "invention," but of the broad claims that he swore to the PTO were his idea, and his alone.

Under the standard articulated by Judge Bryson in *Pernix,* the asserted claims are utterly deficient this is regard.

2. The patents-in-suit do not satisfy the written description requirement for broad, generic patent claims.

In *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (*en banc*),[14] the patent-in-suit contained broad genus claims covering "the use of all substances that achieve the desired result of" inhibiting NF-κB activity. *Id.* at 1341. Although the specification recited the goal of reducing NF-κB activity, the patent at issue did not disclose any "working or even prophetic examples of methods that reduce NF-κB activity, and no completed syntheses of any of the molecules prophesized to be capable of reducing NF-κB activity." *Id.* at 1357-58.

[14] In *Ariad*, the Federal Circuit clarified that § 112 set out two separate requirements – written description and enablement – and that the two were not one and the same, even though, as is true in this case, the findings of fact pertinent to both are largely congruent.

In holding that Ariad's patents failed to satisfy section 112's written description requirement, the Federal Circuit explained that "the hallmark of written description is disclosure." *Id.* at 1351. "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" and "the specification must describe an invention understandable to that skilled artisan and show that the inventor *actually* invented the invention claimed." *Id.* at 1351.

Though the Court stated that "a constructive reduction to practice" can satisfy the written description requirement, *id.* at 1352, it also cautioned that in the context of "genus claims that use functional language to define the boundaries of a claimed genus … the specification must demonstrate that the applicant has made a generic *invention* that achieves the claimed result and do so by showing that the applicant has *invented* species sufficient to support a claim to the functionally-defined genus," *id.* at 1349 (emphasis added).

Recognizing that this was "a problem that is particularly acute in the biological arts," the Circuit explained that the section 112 written description requirement "ensures that when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function." *Id.* at 1352–53.

In the instant case, it is undisputed that the asserted claims are in the biological arts and encompass functional limitations. These functional limitations include (1) pharmacokinetic plasma concentration ranges of the '203 patent and claim 6 of the '321 patent; (2) pharmacodynamic antidiuretic durations of action of the '321 patent and claim 6 of the '203 patent ; (3) and the reduction of the risk of hyponatremia in the '321 patent.

To accomplish these functional limitations, the asserted claims claim a broad range of doses, a broad range of dosage forms, and a broad range of administration routes, all of which

bear on the potential bioavailability, and thereby the PK/PD profile, of the drug in that particular dosage form. It is clear that the claims are broad and generic with respect to all possible combinations encompassed by the claim. Dr. Fein said as much to the PTO. I take him at his word.

But while the table at the top of Column 17 shows that the asserted claims cover a broad range of dosage forms, doses, and administration routes [JX-1-0021 at 17:1-15], the relevant inventive disclosures in the specification relate to just one form (the orodispersible tablet) delivered via one route of administration (sublingually). So this case presents exactly the problem articulated in *Ariad*: "whether the specification provides a sufficient written description of the claimed subject matter, given that the claims cover subject matter far beyond the scope of the embodiment described in the specification and do so in largely functional terms." *Pernix,* 620.

In a recent case that "present[ed] the problem highlighted by the Federal Circuit in *Ariad,"* Judge Bryson of the Federal Circuit (sitting as a trial judge in the District of Delaware) held that the disclosures of the patents-then-in-suit failed to provide adequate written description, because the claims were "broadly cast in generic form," *Pernix,* 323 F. Supp. 3d at 618, 620, and were "far broader than the disclosure," *Id.*, at *628,* while the specification contained "only a single embodiment within the broad scope of the claims." *Id.* at 625. Those are precisely the facts of this case.

In *Pernix,* the asserted claims were limited to an extended release oral dosage form "having hydrocodone bitartrate as the only active ingredient." *Id.* at 575. As Ferring does here, *Pernix* defendant Alvogen argued that the embodiment in the specification did not supply adequate written description support for the asserted claims.

In response, Pernix argued that the common specification described more than just one embodiment, in that it disclosed several different sets of ingredients for the immediate-release component hydrocodone solutions and the modified-release coating solutions. *Pernix*, 323 F. Supp. 3d at 620. Defendant, similar to Ferring here, replied that the specification only identified one embodiment – the tested Devane/Zohydro ER formulation – that actually achieved the functional limitations set forth in the claims (here, of course, Ferring argues that no embodiment achieved the functional limitations set forth in the claims). Defendant in *Pernix* further pointed out that clinical testing would be required in order to determine which if any of the formulations "or any other of the virtually infinite number of potential formulations covered by the claims--would produce the functional results recited in the asserted claims." *Pernix*, 323 F. Supp. 3d at 620.

In invalidating the asserted claims for lack of written description, Judge Bryson credited the testimony of Dr. Mayersohn – who happens to be Counterclaimants' expert in the instant case – when he said:

> [T]he breadth of the claims was not supported by the common specification, which contained only one operative embodiment that was known to satisfy the limitations of the claims. The specification, Dr. Mayersohn testified, did not disclose what combination of components would give rise to the target pharmacokinetic properties in patients … other than the single example set forth in Example 8. The task of creating a formulation that would produce similar results for hepatically impaired and normal patients, he said, would be "a much more difficult challenge." To determine what formulations would work, he testified, would require that each candidate formulation be tested to see if it met the limitations of the asserted claims. He also testified that the common specification was "totally devoid of presentation of structural or formulation characteristics that would allow a person of skill to determine a member of a class such as that described here."

323 F. Supp. 3d at 620–21.

The claims in *Pernix* that Dr. Mayersohn thought not supported by the common specification were far more circumscribed than the asserted claims in the '203 and '321 patents. In *Pernix*, the asserted claims were limited to one route of administration: an oral dosage form. It was in that context that Dr. Mayersohn testified that the breadth of the claims was not supported by the common specification, which contained only one operative embodiment that was known to satisfy the limitations of the claims.

By contrast, the asserted claims of the '203 and '321 patents are far broader. All of the claims apply to *any* transmucosal route of administration and dosage form, including orodispersible tablets, wafers, film and effervescent formulations, eyedrops, suppositories, and enemas. [Trial Tr. 1152:22-1153:1.] Dr. Mayersohn also testified that he also believes the oral tablet is a transmucosal route of administration because of the mucosa in the gut, adding another layer of possible formulations. [Trial Tr. 1154:1-4.]. And some of the asserted claims apply to routes of administration other than transmucosal – intranasal, transdermal, intradermal, subcutaneous, and intravenous – and even to "any method known in the art."

Given the sheer breadth of the asserted claims in this case, the analysis that Judge Bryson found so persuasive in *Pernix* is even more persuasive here. There is simply no way that the disclosures in this case demonstrate that Dr. Fein had invented anything that remotely like the invention claimed in the patents-in-suit. Indeed, the data disclosed in the specification does not include a single example that actually achieved the functional limitations of the asserted claims.

Counterclaimants in this case admit that the common specification does not contain a working example that embodies all of the limitations of the asserted claims, and further admit that a POSITA would be required to engage in clinical testing in order to figure out how much desmopressin in any given form, and via any given route of administration, would yield the PK

and PD parameters required by the patent's claims. However, they assert that the written disclosure requirement is satisfied because the amount of testing required would be "routine." Mayersohn Affidavit ¶ 144; Trial Tr. 1184:15-1185:1.] They also assert that, because desmopressin exhibits linearity in the mean C_{max} of desmopressin at doses above 60 mg in the orodispersible form disclosed in the common specification, a POSITA could calculate the amount of desmopressin needed to achieve at least one of the claimed functional limitations – a C_{max} of no more than 10 pg/ml or 5 pg/ml – by applying a simple formula to the data that are disclosed in the patents. [Mayersohn Affidavit ¶ 69.] Dr. Mayersohn testified that a POSITA could fill the gaps in the disclosure and would thus be able to apply that linearity and project the PK profile of orodispersible sublingual doses below 60 mg. – which is to say, the low doses anticipated by Dr. Fein's "invention." [Mayersohn Affidavit ¶¶ 67-69.]

But the linearity analysis performed by Dr. Mayersohn derives from an extremely limited data set. He posited that a POSITA could calculate the mean C_{max} over all dosage levels of desmopressin administered in sublingual orodispersible form from the data disclosed in Example 7, which was at higher doses than would reliably yield the claimed PK and PD parameters. That data set does not demonstrate that Dr. Fein had possession of more than one dosage form and route of administration. The law is clear that possession of a single embodiment of the claimed invention, within the broad scope of the claims, does not demonstrate that Dr. Fein possessed a generic invention across the scope of those broad claims. *Pernix*, 323 F. Supp. 3d at 626. In light of the analysis in *Pernix,* rooted in principles articulated in *Ariad*, Counterclaimants' argument fails.

Furthermore, desmopressin, as all parties agree, expresses itself in highly variable ways, both inter- and intra-subject. CS004, the actual clinical trial study reporting the C_{max} values set

forth in example 7, reported the coefficient of variation for the mean C_{max} values of the 200, 400, and 800 mg oral dispersible tablets at 55.4%, 77.1%, and 94.9% respectively. Dr. Mayersohn, testified that these coefficients of variations are considered high. [Trial Tr. 53:4-5.] He further testified that, with a coefficient of variation around 40%, due to the high inter and intrasubject variability, one could not say at any given time whether a given individual will achieve a maximum plasma concentration of less than 5 pg/mL or 10 pg/mL for these doses. [Trial Tr. 1172:21-1174:14.]

Therefore, even if one accepts Dr. Mayersohn's testimony that desmopressin is linear for its mean C_{max} across all conceivable doses when administered via ODT and delivered sublingually – and I do – a POSITA would have great particular difficulty predicting, in the absence of individualized data analysis for particular patients, whether the individuals in the example would actually meet the PK parameters claimed in the patents-in-suit. Figuring that out for any individual patient would require testing. [Trial Tr. 38:22-39:10; 165:20-23.] Taken in its best light, Counterclaimants' mean PK linearity argument, and the Examiner's findings with regard to "routine optimization" in favor of written description, stand for the proposition that the patents merely render subsequent inventions obvious. But "a description that merely renders the invention obvious does not satisfy the written description requirement." *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019) (quoting *Ariad*, 598 F.3d at 1352) (internal quotation marks omitted); *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997.) ("The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.")

But there is more.

Dr. Mayersohn's testimony described above addresses only one of the claimed functional limitations. There are two others – duration of action (antidiuresis for 4-6 hours) and reduction of the risk of hyponatremia. Even if Dr. Mayersohn is correct that a POSITA can readily calculate the PK impact of the smaller doses contemplated by the patents-in-suit, desmopressin's inherent variability means that the common specification does not allow a POSITA to know whether Dr. Fein possessed a method for treating individual patients that would meet those other two functional limitations of the claim.

The only disclosure in the common specification that even arguably embodies the full scope of the functional claims (PK and PD parameters) is Example 8. According to Serenity and Reprise, Example 8 "established that the threshold desmopressin blood concentration sufficient to produce an anti-diuresis effect was much lower than the concentrations typically achieved in prior art practice." [DX-35-0003.][15]

However, Example 8 – a study of 8 participants administered a bolus i.v. injection with a bioavailability of 100% of desmopressin over two hours, that mirrors in every meaningful respect Ferring's CS009 study – reports only pharmacodynamic data related to urine osmolality, which purports to show a duration of action of low doses of desmopressin from four to six hours. A POSITA would not find Example 8 an inventive disclosure because it includes no PK analysis by which to assess whether the particular pharmacodynamic phenomenon observed were matched by the claimed plasma concentration ranges. Of course, the patent *says* that both PK and PD were analyzed in Example 8. But that is a lie. The CNF report underlying the data plainly

[15] It is important to note that the patents-in-suit don't claim "*an*" anti-diuretic effect. They claim (1) a maximum blood plasma concentration level of 10 pg/mL or lower for (2) four to six hours (3) while reducing the risk of hyponatremia.

states that neither the duration of action nor PK analyses were performed. [Trial Tr. 420:17-23.] At trial, Dr. Fein admitted that (1) the four to six hour duration of action claimed in the patents was never calculated based on the specified protocol, (2) no PK analysis was performed, and (3) the study he conducted could not provide any information about the PK/PD relationship of low doses and duration of action. [Trial Tr. 420:9-23.]

Even more critically, Example 8 does not actually support the durations of action in the asserted claims, as the findings of fact demonstrate. [FF172-FF184; Trial Tr. 420:13-23, 507:16-19, 508:9-14.] Therefore, a POSITA could not draw any reliable conclusions about the duration of action of other formulations or routes of administration from the data set forth in the patents; she could not even replicate the duration of action claimed in the patent, because of desmopressin's extreme variability and because a POSITA, unlike Dr. Fein, would presumably not drop data in order to calculate a false mean.

Counterclaimants argue that "Based on the studies reported in Example 8 of the specification, Dr. Fein was able to establish that a much lower concentration of desmopressin was sufficient to achieve an antidiuretic effect for a shorter period of time." [CCF ¶ 354.] However, at best, Example 8 only "provide[s] an empirical basis for further clinical studies in patients to evaluate low doses of desmopressin for such conditions as primary nocturnal enuresis, adult nocturia, incontinence and central diabetes insipidus." [JX-1-0026.] And it is well settled that, "Research hypotheses do not qualify for patent protection...." *Ariad*, 598 F.3d 1353.

So the patents-in-suit are directed towards inducing voiding postponement generally or for treating various diseases with voiding disorder indications as long as certain identified PK/PD limitations are met. The asserted claims of the '203 and '321 patents do not recite methods of treatment involving the use of a particular identified formulation – or even a group of

identified formulations – or particular doses of desmopressin. And the asserted claims read on all transmucosal administration routes and all dosage forms therein comprising a dose of desmopressin that meets the PK/PD limitations set forth in the patents – a "genus of formulations [that] incorporates an essentially limitless number of formulation species." *Pernix*, 323 F. Supp. 3d at 618.

All this being so, section 112 requires that the patent disclose either (1) a representative number of species or (2) structural features common to the members of the genus in order to satisfy the written description requirement.

The "structural features" prong of this test can be readily dispensed with. The claims do not identify, and are not limited to, any structural features common to the formulation or dosage forms that would satisfy the functional limitations of the claims. As Dr. Fein himself told the PTO – a point that cannot be repeated often enough – the claims were "*unlimited* with respect to the chemical or mechanical way the concentration profile is achieved." [DX-35-0003 (emphasis added).] At a minimum, the asserted claims, even limited to transmucosal routes of administration, are admittedly broader than the "invention" that Dr. Fein allegedly disclosed to Dr. Nardi, that he described in his testimony during in the *Allergan* trial, and that he testified about at this trial. [Trial Tr. 373:2-15.]

So we turn to whether the broad asserted claims disclose a "representative number" of the species.

Unless one is a "representative" number, they do not.

The common specification purports to disclose, at best, *one* working inventive species – a dose of desmopressin administered sublingually using an orodispersible tablet – that can be shown to induce an antidiuretic effect of less than 10 pg/mL, for four to six hours, while

reducing the risk of hyponatremia.[16] Even that disclosure can only be achieved by extrapolating from the data that is actually disclosed in the common specification – which does not produce any, let alone all, of the functional effects.

The specification provides scant guidance as to which of the other envisioned formulations would satisfy the functional limitations of the claims and which would not. Critically, the common specification does not disclose either a representative number of formulation bioavailabilities or the relationship between bioavailability and administration route. Without disclosing the bioavailabilities of a representative number of forms and administration routes, a POSITA could not be sure about the relationship between the dosage form and the PK/PD profile of the form. And unless the PK/PD profiles claimed in the asserted claims are met, the use of a low dose of desmopressin administered sublingually would not infringe the patents. The Court therefore finds that the specification fails "to distinguish ... infringing methods from non-infringing methods," *Univ. of Rochester*, 358 F.3d at 926; it discloses a species that "only abide[s] in a corner of the genus," and therefore does not "describe[] the genus sufficiently to show that the inventor invented, or had possession of, the genus." *AbbVie Deutschland*, 759 F.3d at 1301.

"Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'— that is, conceive of the complete and final invention with all its claimed limitations — and disclose the fruits of that effort to the public." *Ariad*, 598 F.3d at 1353. Given their breadth, the core problem with the claims is that the specification does not provide sufficient basis for concluding that Dr. Fein possessed a representative number of species falling within the genus that display similar functional features

[16] Example 8 also provides data for a two-hour intravenous infusion, which is not a form a POSITA would use in treatment. [Trial Tr. 871:5-10.]

of the single embodiment. Nothing in the specification would indicate to a person of skill in the art which, if any, of those species (dosage forms) would satisfy the functional limitations of the claims. *See Pernix*, 323 F. Supp. at 628. The specification points to no structural features, other than the sublingual orodispersible tablet, that would assist a person of ordinary skill in the art in identifying species that fall within the asserted generic claims. The patents-in-suit could not disclose only a particular species and "leav[e] it to others to explore the unknown contours of the claimed genus." *AbbVie*, 759 F.3d at 1300.

III. The Asserted Claims Are Invalid for Lack of Enablement under 35 U.S.C. § 112, ¶ 1

A. Legal standards

"The specification shall [also] contain . . . the manner and process of making and using [the claimed invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112(a).

The enablement requirement is separate and distinct from the written description requirement. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351-52 (Fed. Cir. 2009).

"Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (citation omitted).

"The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. The scope of the claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one

of ordinary skill in the art without undue experimentation." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999).

Therefore, "a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012).

Courts may consider several factors "in determining whether a disclosure would require undue experimentation," including: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

"It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement." *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1159 (Fed. Cir. 2019) (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997)).

"A specification that requires a [POSITA] to 'engage in an iterative, trial-and-error process to practice the claimed invention' does not provide an enabling disclosure." *Idenix*, 941 F.3d at 1159 (Fed. Cir. 2019) (quoting *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)).

"Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech*, 108 F.3d at 1366; *see also ALZA*, 603 F.3d at 939-43 (reasoning that the enablement requirement is not met when the specification provides "only a starting point, a direction for further research").

"If mere plausibility were the test for enablement under section 112, applicants could obtain rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded with the spoils instead of the party who demonstrated the method actually worked." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005).

"Simply observing that [a POSITA could make and use the invention]—years after the patent's effective filing date—bears little on the enablement inquiry." *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018).

"The deficiencies in the description as to enablement cannot be cured in [every] case by looking to the knowledge of those skilled in the art at the time of the invention." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (finding an example listed in the specification to be "insufficient" as a working example because it lacked any "bench experiment" demonstrating *functionality* as per the claims).

Further, it is improper to fill gaps in the supporting disclosure with the knowledge of POSITA, because doing so is "an impermissible end-run around the requirement to enable the full scope of the claim." *Idenix*, 941 F.3d at 1159.

If there is no known method and no specific guidance in the specification on how a drug could be administered by a particular route of administration to be effective in treating a disease particularly in a "poorly understood field," claims listing this and other routes of administration may not be enabled. *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1384-86 (Fed. Cir. 2013).

B. Conclusions of Law

1. The asserted claims of the '321 patent and asserted claim 6 of the '203 patent are invalid for lack of enablement because there is no support for the claimed durations of action

CL12. Example 8 in the common specification sets forth an explicit methodology for calculating the duration of action as a function of urine osmolality over time. [FF172-FF14.]

CL13. When the duration of action is calculated based on the explicit methodology set forth in Example 8, the durations of action do not support a duration of action of between about four to six hours, as required by the asserted claims. [FF175-FF178.]

CL14. The urine osmolality data in Example 8 also does not support a duration of action of less than about five hours after administration for urine osmolalities ranging above about 300 mOsm/kg. [FF177-FF178.]

CL15. In view of the faulty guidance in the specification, determining how to treat a patient to achieve the claimed durations of action would require undue experimentation. [FF183-FF184.]

CL16. Accordingly, the asserted claims of the '321 patent and asserted claim 6 of the '203 patent are invalid for lack of enablement because there is no support for the claimed durations of antidiuretic effect. [FF169-FF186.]

2. The asserted claims are invalid for lack of enablement because there is no support for the claimed methods

CL17. The common specification fails to disclose a specific dose or dose range that applies to all dosage forms and routes of administration covered by the asserted claims. As a result the common specification does not provide a practicing physician with enough information to know, without extensive experimentation, which dosage forms, doses, and routes of

administration would achieve the claimed therapeutic effects and other recited properties (*e.g.*, blood plasma concentrations), and which do not. [FF188-FF189.]

CL18. Determining how to treat a patient for the recited conditions using the claimed methods would require undue experimentation. [FF183.]

CL19. Accordingly, all of the asserted claims are invalid for lack of enablement because there is no support for the claimed methods. [FF188-FF189.]

3. The asserted claims are invalid for lack of enablement based on Dr. Fein's admissions in front of the EPO

CL20. Dr. Fein's statements before the EPO regarding the sufficiency of the disclosure in the common specification (i.e., the specification of the '203 patent, referred to as D8 before the EPO during the opposition proceeding for the Eur '821 patent) to support the patentability of the claims constitute admissions against his interest in the validity of the patents in suit. [FF283-FF289.]

CL21. Dr. Fein's admissions before the EPO are evidence that the common specification does not enable one of ordinary skill in the art to make and use the inventions claimed in the patents in suit. [*Id.*]

CL22. Accordingly, Dr. Fein's admissions before the EPO that the common specification does not enable one of ordinary skill in the art to make and use the inventions claimed in the patents in suit render the asserted claims not enabled and invalid. [*Id.*]

C. Analysis

Enablement requires that "the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled when, "at the effective filing date of the patent, one of ordinary skill in the

art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013).

1. Admissions in front of the EPO

In line with the established case law of the European Patent Office (EPO) Board of Appeals, the EPO examination guidelines state that an enabling prior art disclosure "must be such that the skilled person can reproduce that subject-matter using common general knowledge." The guidelines state that:

> Subject-matter can only be regarded as having been made available to the public, and therefore as comprised in the state of the art pursuant to Art. 54(1), if the information given to the skilled person is sufficient to enable him, at the relevant date, to practice the technical teaching which is the subject of the disclosure, taking into account also the general knowledge at that time in the field to be expected of him.

[DX-52-0001 [EPO Guidelines – Ch. IV, Part G, 2] (internal citations omitted) (emphasis added).]

These guidelines make clear that the EPO requires that the disclosure of a prior art document must be sufficient so that the skilled person can reproduce the subject matter for which a document is being cited, using common general knowledge. Only then can that prior art document serve as an invalidating reference against a pending application or a patent subject to an opposition proceeding.[17] It relates to what becomes the general knowledge referred to in the regulation above.

[17] The guidelines provide the following example:

> [A] document discloses a chemical compound (identified by name or by structural formula), indicating that the compound may be produced by a process define in the document itself. The document, however, does not indicate how to obtain the starting materials and/or reagents used in the process. If the skilled person moreover cannot obtain these starting materials or reagents on the basis of common general knowledge (e.g. from text books), the document is insufficiently

The EPO also allows an applicant to argue against the enablement of a prior art reference, arguing that its disclosure does not enable the teaching for which the EPO (or a party to the opposition proceeding) has cited it. Stated differently, an applicant may argue that the disclosure in the prior art does not enable what the EPO or the opponent believes the reference teaches, thus removing that reference from consideration as invalidating prior art. If a document is removed from consideration (because it does not meet the requirements of EPC Art. 83), it cannot then be used to attack the patent on novelty or inventive step grounds.

As noted above (FF283-FF289), Serenity filed a response with the EPO in connection with the opposition proceeding related to the Eur '821 patent. In its response to the Notice of Opposition, Serenity flatly stated, "It is noteworthy that the teaching of [the '203 patent] with respect to the Table in Col. 17 [the table that describes the various routes of administration and dosage ranges that would arguably fall within the claims of the patent] is not enabled, i.e., there is [sic] no examples demonstrating that any of the suggested dose ranges are effective to establish a steady plasma/serum desmopressin concentration in the range of from about .1 picograms desmopressin per mL plasma/serum to about 10.0 picogram desmopressin per mL plasma/serum)." That admission is itself clear and convincing evidence that the patents-in-suit are not enabled.

> disclosed with respect to that compound. Hence, it is not considered to belong to the state of the art according to Art. 54(2) (at least in as far as it relates to that compound) and consequently it does not prejudice the patentability of the claimed invention.
>
> If, on the other hand, the skilled person knows how to obtain the starting materials and reagents (e.g. they are commercially available, or are well-known and appear in reference text books), the document is sufficiently disclosed with respect to the compound and therefore belongs to the state of the art according to Art. 54(2)."

[DX-38, EPO Guidelines for Examination – Ch. IV, Part G.]

Counterclaimants are absolutely correct that the purpose of Serenity's response was to note that the '203 patent specification did not negate the novelty of the NOCTIVA spray device. Serenity's argument was, in fact, that EUR '821 was an improvement patent, and that it therefore provided an inventive step over the teachings of the prior art. *See* [DX-38, 11.28] But that does not change the fact of what was said in the text of the Response. In articulating the various limitations of the '203 patent's specification, Serenity flatly stated that the teaching of the '203 patents in Table 17 – the table that set out the various transmucosal methods of administration that Dr. Fein contended were covered by the patent, together with (rather broad) dosage ranges that would arguably fall within the patent for each mode of administration – was "not enabled." [DX-38-0044 at ¶ 11.14.]

There can be no suggestion that this admission does not doom the patents-in-suit because of differences between U.S. and EU patent law with respect to the term "enablement." In both systems, when the enablement of a cited reference is questioned, it is only with respect to the teaching for which that reference is cited. The relevant inquiry is not whether a cited reference would enable the invention claimed in the pending application or patent subject to opposition. The inquiry does not relate to whether prior art references enable *those* pending applications or patents subject to opposition proceeding. The EPO guidelines cited above do *not* relate to enablement of pending applications or patents subject to opposition proceeding by the prior art. Instead, the guidelines relate to the enablement of the disclosures in the prior art such, such that the prior art either is or is not an invalidating reference.

Serenity's argument to the EPO was about the sufficiency of the disclosure of D8 ('203) for the teachings of that very patent – the '203 patent here whose validity is at issue here. Whether the 'Eur 821 patent is enabled (i.e., has a sufficient disclosure) is a completely different

issue. The admissions in the Response to Opposition – admissions that the D8 ('203) patent did not enable its own invention, and that a POSITA would have to embark on a "research program" in order to use the claimed invention – relate to the enablement of the '203 patent, not the Eur '821 patent. And as will be discussed in far more detail below, Serenity's past statements about the limitations of the common specification apply with equal force here.

D. The Wands Factors

Even if Dr. Fein's admission to the EPO were not enough to establish lack of enablement, Ferring has demonstrated, by clear and convincing evidence, that, at the time of the filing date, a person of ordinary skill in the art would not be able to practice the claimed invention without undue experimentation. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014) (quoting *In re Wands*, 858 F.2d at 736–37).

In analyzing undue experimentation, the Federal Circuit considers factors such as: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1345–46 (Fed. Cir. 2019) (citing *In re Wands*, 858 F.2d at 737.)

Regarding the second and third factors – the amount of guidance presented and the presence or absence of working examples – as established in the above analysis of the written description requirement, there is – at best – one working example within the broad scope of the claims; and Dr. Fein admits that this one working example "could not provide any information about the pharmacokinetic/pharmacodynamic relationship of low doses and duration of action," though that was required by the research study protocol. [Trial Tr. 420:19-23; *see* DX-22.]

As for factors 4 and 8 – again, as was established in the findings and conclusions relating to written description – the scope of the asserted claims is quite broad, particularly in light of the purported invention. The invention and asserted claims relate to methods of treatments for various diseases by transmucosal administration generally, encompassing any dosage form, and any dose, as long as it meets the functional limitations of the claims. According to Dr. Fein, the claim of transmucosal administration represents "a broadened version" of what he originally asserted as his invention, which was sublingual (not all transmucosal) administration. [Trial Tr. 373:7-12.]

Regarding the sixth factor, the minor differences in the parties' definition of a POSITA does not meaningfully change the analysis, as both sides agree that the relative skill of those in the art is high.[18]

As to the seventh factor, predictability of the art, it is undisputed that, with regard to desmopressin, there is high intra- and intersubject "variability and sometimes very large variability in the response to a given drug among patients in the population." [Mayersohn Affidavit ¶ 45.] Dr. Mayersohn also testified that, owing to the tremendous pharmacokinetic and pharmacodynamic intersubject and interpopulation variability characteristic of desmopressin,

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[18] Serenity and Reprise urge that a POSITA at the time of the invention would include an individual having an M.D. or Pharm.D or Ph.D. degree in pharmacology, pharmaceutics, or other related discipline, with knowledge in the field of pharmacokinetics and pharmacodynamics. The POSITA should further have an understanding of, or experience in, conducting human clinical drug trials. [Murray Rebuttal Affidavit ¶ 14.]

Instead of a single individual, Ferring contends that a person of ordinary skill in the art for the asserted claims of the patents in suit would be a team of individuals. This team would include a physician with a medical degree, as well as experience in diagnosing, treating, and/or prescribing medication to treat patients who are in need of voiding postponement. The team would also include an individual with an advanced degree (e.g., a Ph.D. or Masters or PharmD or equivalent) in one of the pharmaceutical sciences and three to five years of experience in clinical pharmacology or drug formulation. [Spaans Affidavit ¶ 55.]

and particularly at the ranges and CV% disclosed in the Example (i.e., unpredictability), a POSITA could not predict whether any given patient would achieve the PK parameters without testing. [Trial Tr. 38:13-39:10.] In fact, Dr. Mayersohn testified that, "Nobody can do that. Nobody knows how to do it. It's never done." [Trial Tr. 39:8-10.][19]

As Serenity and Reprise's expert, Dr. Murray testified, desmopressin is a synthetic peptide molecule and "we're not talking about a standard drug, we're talking about replacing a hormone" and "trying to mimic a biologic condition." [Trial. Tr. 212:9-14.] Regarding this biologic system, he further testified that "there's big variation in the response of [desmopressin] across the spectrum" and "in hormonal systems where we're looking at a picogram and nanogram levels, the amount of hormone it takes to make variation is a tiny amount, but it has … a physiological effect." [Trial Tr. 236:4-20.] It is clear that the patents-in-suit belong to an unpredictable art.

Finally, as to the first and decisive factor, the quantity of experimentation necessary: the parties do not disagree that experimentation would be necessary for a POSITA to practice the claimed invention. Their dispute is over just how much experimentation is needed to enable the full scope of the claims. As the above findings of fact make clear, I conclude that it would be so extensive as to qualify as undue experimentation.

In this context, *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019) is instructive. There, plaintiff Idenix brought a patent infringement suit against defendant Gilead for infringement of the claimed method of treating Hepatitis C (HCV) by

[19] It is indeed "never done" when applying for FDA clearance to bring a new drug to market; reliance on mean data is the norm. However, we are not talking about the standards for new drug approval in this patent case; we are talking about whether the invention sufficiently enables a POSITA to practice the claimed invention in a patient. That, as *Pernix* makes clear, is judged by a different standard.

administering a nucleoside compound having a particular chemical and stereochemical structure. 941 F.3d at 1154. Specifically, the patent's disclosure centered on one class of "2'-up compounds": those having a hydroxyl group (OH) at the 2'-down position. *Id.* at 1155.

In upholding the District Court's grant of judgment as a matter of law for defendant on the issue of nonenablement, the Federal Circuit found that the quantity of experimentation necessary was high and weighed in favor of nonenablement because, while the patent claimed all 2'-methyl-up compounds effective against HCV, the "patent encompass[ed] at least many, many thousands [of compounds] which need to be screened for HCV efficacy," *id.* at 1159, and "the only working examples provided [were] exceedingly narrow relative to the claim scope," *id.* at 1161. Indeed, the Court of Appeals concluded that, "the evidence presented to the jury could not support any other finding." *Id.* at 1155. Further, the quantity of experimentation was high even if the synthesis of any particular compound was a routine exercise, "Due to the unpredictability of the art." *Id.* at 1162.

In the instant case, while the disclosures of the patents-in-suit center on one particular compound that purports to meet the functional limitations of the claims – the sublingual orodispersible tablet – the asserted claims encompass all transmucosal dosage forms, and some of them include transdermal, subcutaneous, intradermal, intranasal and intravenous formulations as well. [JX-17-0021 at 17:9-12.] The specification is far narrower than the asserted claims, and it is undisputed that experimentation is required to use the many thousands of possible formulations – at least 14,000 for just transmucosal administration – that purport to reach the functional limitations of the claims. [Trial Tr. 1154:9-1157:10; 1183:11-1185:1.] *See Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013) (finding of nonenablement as a matter of law notwithstanding the fact that screening an individual

compound for effectiveness was considered "routine" because there were "at least tens of thousands of candidate compounds" and "it would be necessary to first synthesize and then screen each candidate compound" to practice the full scope of the claims).

On this score, this case is quite unlike *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180 (Fed. Cir. 2014), on which Serenity and Reprise rely. There, the court found determinative that Defendants "failed to make the threshold showing that any experimentation is necessary to practice the claimed methods" and the district court erred "because its enablement analysis did not address that determinative question." *Id.* at 1186. In the instant case, Counterclaimants' own expert testified that at least some range of testing would be required to practice the claimed methods. [Trial Tr. 38:13-39:10; 1183:10-20.][20] Indeed, Counterclaimants *own expert* testified

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[20] The case is distinguishable on nearly every other ground. In *Alcon*, the claimed methods "comprise[d] only a single step—adding a chemically-stabilizing amount of PECO to the prostaglandin composition—that [Defendants'] own expert testified was routine." 745 F.3d at 1189 (internal quotations omitted). Those claimed methods required only that the addition of PECO to the composition "provide *some* increase in chemical stability" and did "*not* require a particular level of stability or a particular magnitude of increase." *Id.* (emphasis added). The claims before us are far more demanding. In sharp contrast to the "single step" that only required "*some*" effect, the claims here involve administering a compound of desmopressin through every transmucosal route, in a wide range of doses, and a wide range of dosage forms. Crucially, the asserted claims *require* "a particular level" of desmopressin plasma concentration, and others, a particular pharmacodynamic result.

Additionally, in *Alcon*, "the patents (1) disclose[d] exemplary compositions within the scope of the claims, (2) detail[ed] how those example compositions are prepared from commercially-available ingredients, and (3) provide[d] step-by-step procedures for adding PECO to a prostaglandin composition in a way that embodies the claimed invention." *Alcon Research*, 1189. Here, instead of disclosing multiple compositions, the patents-in-suit rely on one composition – at best – and there are serious questions whether it itself meets the full scope of the claims. Second, the patents' common specification does not detail how any other representative compositions are prepared. Third, the patents' common specification are a far cry from offering step-by-step procedures for achieving the PK/PD limitations using the wide range of doses, in the wide range of administration routes, in the wide range of administration forms, and for the group of clinical indications *including* the general goal of inducing an antidiuretic

that bioavailability – the necessary prerequisite to Plaintiff's proportionality equation -- "is determined in an experiment, for example, where you administer one dosage form compared to intravenous or to another dosage form." [Trial. Tr.1186:7-11.] So, unlike the Plaintiffs in *Alcon*, Counterclaimants could not credibly contend that no experimentation is required to practice the claims: they assert only that any experimentation necessary would be "routine." And of course, Ferring vigorously contests that assertion.

Assuming *arguendo* that the patents enable a POSITA to practice the administration of desmopressin via a sublingual orodispersible formulation, that would only be one embodiment among many encompassed by the broad scope of the claims. Given (1) the unpredictable nature of the art, (2) the broad genus claimed – being unlimited with respect to dose or dosage form and curtailed only by functional limitations – and (3) the lack of other examples, this single embodiment is not enough to enable the full scope of the claims. In the context of these asserted claims, section 112 is more demanding.

Serenity and Reprise urge the Court to conclude that its single disclosure of a single embodiment is sufficient because, in *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991), the Federal Circuit said that, "The enablement requirement is met if the description enables *any* mode of making and using the claimed invention." Unfortunately for Counterclaimants, that single sentence is not the entirety of the rule of *Engel.*

It is true that the Federal Circuit has articulated the principle that the disclosure of a single embodiment of the claimed invention is sufficient – but only if it allows a POSITA to practice the scope of the claimed inventions without undue experimentation. *See, e.g.*, *Spectra*

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effect generally. In short, it is quite clear that the common specification of the patents-in-suit is simply far less robust than was before the court in *Alcon.*

Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1533 (Fed. Cir. 1987). Serenity and Reprise hang their hat on a distortion of this principle that frustrates the purpose of section 112.

In *Spectra Physics*, the Federal Circuit indicated that disclosure of a single embodiment would only allow the POSITA to practice the full scope of the claimed invention without undue experimentation when the invention "….pertains to an art where the results are predictable, e.g., mechanical as opposed to chemical arts." *Spectra*, 827 F.2d at 1533. Only then can it be "enabled by disclosure of a single embodiment and is not invalid for lack of enablement simply because it reads on another embodiment of the invention which is inadequately disclosed." *Id.* In *Spectra*, the Federal Circuit thus limited when the disclosure of a single embodiment could satisfy the enablement requirement to arts "where the results are predictable," such as the mechanical arts. *Id.*

Plaintiffs cite to a subsequent mechanical arts case, *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991), for the proposition that the "enablement requirement is met if the description enables any mode of making and using the claimed invention." *Id.* In *Engel*, the asserted claims encompassed a method for connecting the ends of sheet metal ducts. *Id.* at 531. There, the court rejected defendant Lockformer's section 112 argument that the patents were invalid for lack of enablement because, though the specification disclosed a method of "snapping" the device together, it failed to disclose a method of connecting the ends called "crimping," which defendants argued was the "best mode" of connecting the ends.

The lion's share of the court's analysis was directed to the "best mode" requirement; the court gave comparatively short shrift to Lockformer's enablement argument. It simply rejected the contention, citing (without further discussion) to *Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923, 929 (Fed. Cir. 1990) for the proposition that, "The enablement requirement is met

if the description enables any mode of making and using the claimed invention." *Engel*, at 1533. But *Chemcast* was not an enablement case. The issue before the *Chemcast* court was whether the section 112 "best mode" requirement had been met.[21] It was not, as *Engel* implies, discussing the entirely separate enablement requirement. *See Chemcast*, 913 F.2d at 926 (drawing the "critical distinction between" the enablement and best mode requirement, and then commencing to analyze only the best mode requirement). Given the "critical distinction" between the doctrines, *Chemcast*, 913 F.2d at 926, it is curious that the *Engel* court cited to *Chemcast* – especially since the court in *Spectra Physics* had limited the application of the "any mode" rule to the predictable arts, a restriction not even mentioned in *Engel.*

There is no suggestion in subsequent Federal Circuit jurisprudence that *Engel* was meant to overturn or broaden *Spectra Physics*. Indeed, in *Engel*, the invention was a mechanical one that fell squarely within the range of the predictable arts: a method for connecting the end of sheet metal ducts. Nonetheless, other Federal Circuit cases over the years, in both the predictable and unpredictable arts – including mechanical and biological arts cases – have relied upon the holding in *Engel* that "*any* mode of making and using the claimed invention" is sufficient to satisfy the enablement requirement.

Plaintiffs cite to one such case, *CFMT, Inc. v. Yieldup Int'l. Corp.*, 349 F.3d 1333 (Fed. Cir. 2003) for the proposition that "Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment of the invention absent a claim limitation to that effect," *see id.* at 1338. There, the enablement

[21] Patent invalidity for failure to set forth the best mode requires that (1) the inventors knew of a better mode of carrying out the claimed invention than they disclosed in the specification, and (2) the inventors concealed that better mode. *Chemcast Corp. v. Arco Indus. Corp.*, 913 F.2d 923, 927–28 (Fed. Cir. 1990).

requirement was satisfied where the specification included a single method of making and using the claimed invention – a semiconductor wafer cleaning system. *See CFMT*, 349 F.3d at 1338.

Aside from the fact that *CFMT*, like *Engel*, was a case that arose in the context of the mechanical/predictable arts, Serenity/Reprise's reliance on *CFMT* is misplaced for several reasons.

In *CFMT*, the representative claims were directed at improvements to a system for the cleaning and treatment of semiconductor wafers. *Id.* at 1335. Plaintiff CFMT sued Defendant YieldUp for infringement of two patents. In defense, YieldUp asserted, *inter alia*, that the patents were invalid as nonenabled and moved for summary judgment on the issue of enablement. *CFMT*, 349 F.3d at 1336. YieldUp's nonenablement argument hinged on the difficulties CFMT faced in installing a commercial embodiment of the cleaning and treatment system for Texas Instruments (TI). The record indicated that the system did not meet TI's particular commercial standards, and that the inventors had to tinker with their invention over the course of months before the company was satisfied. *Id.* at 1336.

In granting summary judgment in YieldUp's favor, the district court held that "the system that was based on the [patents] could not clean wafers, [and] that the inventors experimented with the Full Flow system for more than six months, and that the solution to the problem eventually resulted in [a subsequent patent] demonstrates that the experimentation required ... was not routine." *Id.*, at 1336-37 (internal quotations omitted).

On appeal, the parties did not dispute that the record showed CFMT's initial efforts to build a *commercially* viable machine that carried out the steps of the claimed methods required undue experimentation. 349 F.3d at 1338 Rather, the issue before the Federal Circuit was whether the claims required a specific level of cleanliness and contaminant removal *at all* and

whether the subsequent improvements to the invention showed that the patents did not enable the full scope of the claimed invention. *Id.* at 1338.

On these questions, the Federal Circuit reversed and remanded. The court instructed that, given the nature of the claims, the proper question was whether the disclosures taught "*any* level of cleaning with the claimed invention without undue experimentation," because the claims in the patents stated no particular standard of cleaning. *Id.* In essence, the court determined that the district court erred in setting TI's particular commercial standards for cleanliness as the bar by which to judge enablement "absent a claim limitation to that effect." *Id.* In the absence of such a claim limitation, "any meaningful cleaning would satisfy the claimed goal of cleaning of semiconductor wafers." *Id. at* 1340 (internal quotations omitted).

The Federal Circuit the court was careful to cabin the holding in *CFMT* to the facts of that case. Indeed, in citing to *Engel* for the "any mode" rule, the court noted that "when an invention claims a *general* system to improve … the disclosure enables that invention by showing improvements in the overall system." *Id.* at 1338 (emphasis added). However, the court went on to explain, "Of course, if a patent claimed a system that achieved cleanliness up to a specified numerical [] range, then enablement would require disclosure of a method that enables one of ordinary skill to achieve that range without undue experimentation. Thus, the level of disclosure necessary to satisfy [the enablement requirement] varies according to the scope of the claimed invention." *Id.* (citing *Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1306-07 (Fed. Cir. 2001).

CFMT merely reinforces the conclusion that, for the specifications of the patents-in-suit to be enabled, they must allow a POSITA to achieve the particular PK and PD ranges claimed, which turn out to closely align with effective clinical (and, coincidentally, commercial) ranges.

[Trial Tr. 508:9-24.] Rather than claiming antidiuretic effects of desmopressin generally, the asserted claims of the '321 patent, and asserted claim 6 of the '203 patent, claim the administration of an unspecified amount of a desmopressin pharmaceutical composition that will achieve specific and particular numerical ranges for both pharmacokinetic desmopressin plasma concentration ranges and pharmacodynamic durations of actions. The other asserted claims of the '203 patent all require a particular plasma/serum desmopressin concentration range. Rather than shielding the patents-in-suit from scrutiny by any commercial standards, *CFMT* explicitly holds that enablement might require a commercially viable embodiment when there are claim limitations to that effect. *Id.* at 1338. And they must do so "according to the scope of the claimed invention," *id.*

A 2012 biotechnology case, *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269 (Fed. Cir. 2012) is the most recent Federal Circuit case where disclosure of a single embodiment was found to satisfy the enablement requirement. In *Streck*, it was undisputed that the patents-then-in-suit enabled one and only one mode of using the claimed invention: analog reticulocyte integrated controls. *Id.* at 1287. Defendants argued that for the full scope of the claims to be enabled, the patents had to also enable the use of *true* reticulocyte integrated controls.

As should be obvious, *Streck* is instantly distinguishable. The scope of the claims spanned a class of just two compounds: true reticulocyte integrated controls and analog reticulocyte integrated controls. In the instant case, the asserted claims encompass a potentially unlimited class of possible formulations and compounds that could meet the functional limitations of the asserted claims. *See* [Trial Tr. 1154:8-1157:8; Ferring Demonstrative 11.]

Moreover, in rejecting defendant R&D's argument, the court found that true reticulocytes and analog reticulocytes "work in exactly the same way" and "are virtually indistinguishable." *Id.* at 1289. The court essentially determined that there was no functional difference between the two types for the purpose of enablement. Therefore, enabling one was enabling the other.

Here by contrast, each variation of a compound containing desmopressin, and each administration route, changes the bioavailability of desmopressin and therefore, both the pharmacokinetic and pharmacodynamic profile of the form and administration route. These variations all bear on whether the form meets the functional limitations of the claims. At the very least, bioavailability depends on the formulation, the dosage form, the method of manufacture, and the excipients used. And as Serenity and Reprise's own expert testified, "Bioavailability is determined in an experiment." [Trial Tr. 1186:7-12.] There is no evidence that all of these different formulations "work in exactly the same way" as the single example disclosed in the patents-in-suit; on the contrary, all the testimony at this trial suggests that the myriad claimed formulations would work very differently, both from each other and in different patients.

A rule that limits the "any mode of making and using the claimed invention" to the predictable arts is more faithful to the bargain struck by section 112. In exchange for the right to exclude others from practicing the invention for the duration of the patent's terms, a patent holder is obligated to "ensure[] that the public knowledge is enriched by the patent specification to a degree *at least* commensurate with the scope of the claims." *Crown Operations Intern., Ltd. V. Solutia Inc.*, 289 F.3d 167, 1378-1379 (Fed. Cir. 2002) (citing *Nat'l Recovery Techs., Inc. v Magnetic Separation Sys.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999)) (emphasis added.) The broader the right of exclusion, the broader the teachings should be. Therefore, reading the cases in harmony might suggest that *Engel* – a case in which the invention was a mechanical one, and

hence fell within the "predictable arts" – articulates a rule that is limited to the context of the predictable and mechanical arts.

The patents-in-suit belong to the line of cases like *Idenix* in the *unpredictable* arts where the Federal Circuit has made clear that section 112's enablement requirement must be commensurate with the scope of the claims.[22] In these cases, the Court of Appeals has repeatedly reinforced that claims fail for lack of enablement – even when a single embodiment is disclosed – where the disclosure fails to demonstrate how to make and use the *full* scope of the claimed invention.

In *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247 (Fed. Cir. 2004), a biotechnology case, the scope of the claim included at least two different types of monoclonal antibodies – murine and chimeric.[23] Though the disclosures "certainly enable[d] murine antibodies," they did "not enable chimeric antibodies." *Id.* at 1256. Plaintiffs argued that at the date of the application, "chimeric antibodies were so well known that they had become routine technology" and that the disclosures "need not specifically enable chimeric antibodies, because technicians of ordinary skill in the art could make and use them by that time without undue experimentation." *Id.* at 1256. In rejecting this argument, the Court found the asserted claims invalid for lack of

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[22] To be sure, these cases also involve technical fields in the predictable arts. To wit, the 2007 mechanical case *Automotive Technologies International, Inc. v. BMW of North America, Inc.*, 501 F.3d 1274, 1276-1277 (Fed. Cir. 2007) involved a side-impact sensor for airbags. The claims there were construed more broadly than the example disclosed. The Court found that practicing the full scope of the claimed invention would require undue experimentation, explaining that knowledge of one skilled in the art could not supply the missing information because the specification, not the knowledge of those skilled in the art, must supply novel aspects of the invention. *Id.* at 1283. This decision arguably stands in stark contrast to the "single embodiment" line of cases in the mechanical arts where the knowledge of one of ordinary skill can be used to fill any perceived deficiencies in the disclosure.

[23] Murine antibodies are derived from mouse cells, whereas chimeric antibodies combine DNA from multiple species. *Chiron*, 363 F.3d at 1250.

enablement because the disclosure fell short of providing a "specific and useful teaching" of all antibodies within the scope of the claim. 363 F.3d 1247, 1254-1256 (Fed. Cir. 2004.)

Similarly, in *Monsanto v. Syngenta*, 503 F.3d 1352 (Fed. Cir. 2007), the court held asserted claims of a patent invalid under § 112 because the specification did not enable the full scope of the broad functional language in the asserted claim without undue experimentation. *Id.* at 1360-1362. There, the asserted functional claim was construed to require the claimed gene to function in any plant cell, including both dicots and monocots.[24] 503 F.3d 1352, 1361 (Fed. Cir. 2007.) Even if the specification enabled dicots, it did not enable monocots because the method of using monocots was not then known in the art and thus, the Court found that practicing the full scope of the invention would require undue experimentation. *Id.*

Notwithstanding the clear requirements of section 112, Dr. Mayersohn testifies that disclosure of the single embodiment enables the full scope of the claims (i.e., allows a POSITA to practice the claimed invention for other dosage forms and administration routes), because a POSITA could "create a simple proportionality relating the values of bioavailability for each route of administration to arrive at the dose needed for the new route of administration." [Mayersohn Affidavit ¶ 34.] This "simple proportionality equation" was $Dose_2 = F_1/F_2 * Dose_1$, where F_1 and F_2 are different routes of administration.

But the patents-in-suit do not disclose the bioavailabilities for each route of administration. Simply uncovering that would require numerous clinical trials.

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[24] "Flowering plants can be broadly categorized as monocotyledons ('monocots') and dicotyledons ('dicots'), depending on whether the initial development of the seed produces one leaf (monocot) or two leaves (dicot)." *Monsanto*, 503 F.3d at 1361(quoting *Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1338 (Fed. Cir. 2003)).

Second, while I accept Mayersohn's testimony that the mean C_{max} of the orodispersible tablet is linear below 60 mcg, the differences in bioavailability among various formulations and routes of administration of the drug means that a POSITA would not know, without experimentation, what dose would be effective to yield the claimed plasma concentration ranges if the drug were administered via the other claimed administration routes and forms. The asserted functional claims must be achievable by any transmucosal route of administration, including buccal and sublingual (orodispersible tablets, wafers, film and effervescent formulations), conjunctival (eyedrops), and rectal (suppository enema). [JX-1-0021 at 17:9-12.] Each of the different types of transmucosal administration require vastly different formulations and excipients. For example, eye drops are a liquid formulation, while orodispersible tablets and wafers are solids. Even within the same formulation type, there are a variety of excipients that a POSITA may choose, all bearing on the characteristics of the form. Even if *the same* excipients were used, the volume of those excipients in both absolute terms and relative to other excipient may differ, again, bearing on the PK/PD profile of the form. [Spaans Affidavit ¶ 87.] So the fact that a POSITA could use the data disclosed in the patent to calculate a lower dose for a the sublingual ODT that would yield a mean Cmax within the claimed range (below 10 pg/mL or 5 pg/ML) does not solve the enablement conundrum, or eliminate the need for experimentation rising to "undue" levels.

There is yet another flaw in Dr. Mayersohn's approach. The orodispersible form disclosed in the specification is only linear as to PK parameters – not PD parameters – so demonstrating linearity of the C_{max} of the orodispersible form at low doses does not help a POSITA to achieve the claimed durations of action in a patient without a great deal of experimentation.

Finally, even if disclosures in the specification reduce the amount of experimentation necessary to administer the sublingual dosage form, the specification does not provide useful teachings with regard to the required pharmaceutical composition of other dosage forms and administration routes, and does not disclose their bioavailabilities, and thus, their unique pharmacokinetic and pharmacodynamic profiles. As Ferring pointed out in a particularly graphic analysis, Table 17 (the table that Serenity said was "not enabled" in front of the EPO) encompasses at least 14,000 possible embodiments, even given certain limiting assumptions about the number of excipients that would have to be used in order to create a desmopressin formulation that could be administered to a patient (4). [Trial Tr. 1154:8-1157:8; Ferring Demonstrative 11.] Ferring has presented clear and convincing evidence that Dr. Fein's decision to dramatically expand the scope of his claims far beyond his purported sublingual orodispersible invention as originally conceived renders any suggestion that he has enabled dosage forms and administration routes across that broad scope incredible.

In order to practice the claimed invention for any given claimed desmopressin dosage form and administration route, a POSITA would have to select from amongst the thousands of formulation possibilities claimed in the patents. Even making the threshold determination of which dosage form to use would require testing. [Trial Tr. 1154:8-1157:8.] As Dr. Mayersohn testified, a skilled POSITA would have to "come up with a dosage form for in vitro testing, perhaps half a dozen formulations, and then test it in animals, if you have an animal model, or if not" a "well-designed study in a half a dozen subjects if that's necessary, and then you go on from there. You keep iterating." [Trial Tr. 1183:11-20.] Though Dr. Mayersohn testified that drug companies have a "general library of formulas that work for them," he further testified that

these companies have not necessarily done this type of formulation work with desmopressin. [Trial Tr. 1184:15-1185:1.]

Only after doing this could a POSITA think about attempting to "relate the bioavailabilities." And though Dr. Mayersohn testifies that "With respect to other routes of administration, it would be a matter of routine experimentation for a POSA to determine the bioavailabilities," [Mayersohn Affidavit ¶ 114], that testimony is completely undermined by his subsequent admission that that experiment would be "very similar to what is disclosed in Examples 7 and Comparative Example 4," both of which are based on Ferring's *clinical studies* testing the absolute bioavailability of the orodispersible sublingual tablet and oral tablet respectively. [JX-1-0022 at Ex. 7; JX-1-0022 at Comparative Example 4.]

The dose proportionality equation Mayersohn proposes *requires* and *assumes* knowledge about the bioavailabilities of both doses and administration forms. [Mayersohn Affidavit ¶ 34.] Dr. Indeed, as Dr. Mayersohn further testified, "Bioavailability is determined in an experiment, for example, where you administer one dosage form compared to intravenous or to another dosage form. You determine the areas under the concentration time curve, and now you have measured bioavailability. You don't have data like this to do to [a proportionality calculation.]." [Trial Tr. 1185:19-1186:12.] Mayersohn's characterization of the experimentation necessary being "routine" is simply not convincing in light of his attendant admission that, in order to use other dosage forms, a POSITA would have to conduct clinical studies, like CS004 and Comparative Example 4. [Mayersohn Affidavit ¶ 114.]

Counterclaimants assume that POSITAs will simply supplement the inadequacy in the patent specification with their own knowledge. [Trial Tr. 1138.] However, it is the specification that provides written description support, not the knowledge of a POSITA. While a specification

need not disclose what is well known in the art, "that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Id.*

A POSITA could not perform any of what Serenity and Reprise call "routine experimentation" based on Dr. Mayersohn's proportionality equation until s/he determined what the bioavailability of the dosage form was, and its particular interaction with the chosen administration route. And until a POSITA tests a given dosage form to figure out what its bioavailability is, the linearity of the mean C_{max} of the highly variable (from patient to patient) orodispersible dosage from – on which Counterclaimants hang their hats – is absolutely irrelevant.

These arguments apply *a fortiori* to the individual level of treating "a patient," with his/her particular and potentially highly variable response to desmopressin. But treatment of "a patient" is what the patents-in-suit claim. Dr. Mayersohn further admitted that, due to its variability, a POSITA could not know whether a person would have a plasma concentration within the claimed ranges without testing, [Trial Tr. 38:13-39:10], and that because of its high degree of variability, doses necessary to treat different voiding disorders and for different patient populations are different. [Mayersohn Affidavit ¶ 83; Verbalis Affidavit ¶ 30.]

Indeed, as Counterclaimants' other expert, Dr. Murray, testified, "we're not talking about a standard drug, we're talking about replacing a hormone." [Trial. Tr. 212:3-14.] In "hormonal systems where we're looking at picogram and nanogram levels, the amount of hormone it takes

to make variation is a tiny amount . . . ." [Trial Tr. 236:4-20.] Any variation in the dosage form, within all the transmucosal administration routes, including buccal and sublingual (orodispersible tablets, wafers, film and effervescent formulations), conjunctival (eyedrops), and rectal (suppository enema), would result in fundamental changes to both the pharmacokinetic and pharmacodynamic profile of the dosage form.

The common specification provides only a target for further research. A POSITA would still have to conduct extensive the experimentation to arrive at a form that meets the claimed functional limitations. Given the number of different dosage forms and formulations that are encompassed only within the transmucosal route of administration, this would clearly amount to undue experimentation. The human endocrine system is not a predictable machine.[25] Since the *Wands* factors decidedly establish that practicing the patents-in-suit would require undue experimentation, the asserted claims are not sufficiently enabled.

IV. The Patents in Suit Are Invalid under 35 U.S.C. § 102(f) Because Dr. Fein Himself Is Not the Inventor of the Subject Matter of the Patents-In-Suit

A. Legal Standards

An applicant is not entitled to a patent if "he did not himself invent the subject matter sought to be patented" 35 U.S.C. § 102(f).

A patent must accurately name the correct inventors of a claimed invention. *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1349 (Fed. Cir. 1998).

A determination of "statutory invalidity due to improper inventorship … need not be accompanied by the names of the supposed correct inventors. A patent may be invalid simply

[25] The FDA recognized this in particularly dramatic fashion by requiring the "black box" warning described in FF 276, *supra.*

because it names the wrong inventors." *Belcher Pharm., LLC v. Hospira, Inc.*, No. Cv 17-775-LPS, 2019 WL 2503159, at *1 n.1 (D. Del. June 5, 2019) (citing *Pannu*, 155 F.3d at 1349).

An "inventor's statements made during the course of litigation might in some circumstances justify a court in concluding that the named inventor 'did not himself invent the subject matter sought to be patented,' 35 U.S.C. § 102(f)." *Id.*

"Determining 'inventorship' is nothing more than determining who conceived the subject matter at issue, whether that subject matter is recited in a claim in an application or in a count in an interference." *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994).

Conception is a question of law premised on underlying factual findings, *see In re VerHoef*, 888 F.3d 1362, 1365 (Fed. Cir. 2018), and a person is not a sole inventor where their "sole contribution … was known in the prior art." *Belcher*, 2020 WL 1650535, at *23-24.

"[A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007) (citing *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

Conception "requires more than just a general goal or research plan, and instead requires a definite and permanent idea of an operative invention, including ***every feature*** of the subject matter to be patented." *In re VerHoef*, 888 F.3d at 1366 (Fed. Cir. 2018) (internal quotation marks omitted).

When all an inventor has is a "hope, or wish" in their claim to the result of a biological process, "Such a bare hope is insufficient to establish conception." *Hitzeman v. Rutter*, 243 F.3d 1345, 1356-57 (Fed. Cir. 2001).

B. Conclusions

CL23. Dr. Fein is not the inventor of the inventions claimed in the patents-in-suit.

CL24. At the very least, Dr. Fein was not the sole inventor of the inventions claimed in the patents-in-suit.

CL25. The patents-in-suit are invalid in that they do not accurately name the correct inventors of the claimed invention, *Pannu*, 155 F.3d at 1349, there being clear and convincing evidence that Dr. Fein "did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f).

C. Analysis

The conclusions of law are compelled by Findings of Fact ¶¶ 79-111, which are set forth above. To the extent that Dr. Fein invented anything at all, he did so in conjunction with scientists at Ferring – as he himself admitted when he gave Ferring's patent attorney an inventorship memo that described in his own words his rather limited contribution to the GB patent application filed by Ferring on May 1, 2002.

Overwhelming evidence demonstrates that the concept that a low dose of desmopressin administered via orodispersible tablet to treat voiding disorders (specifically nocturia in the elderly) was an idea that had been worked on by others, notably at Ferring, for many years before Dr. Fein had anything to do with research into those issues. Contrary to his absolutely incredible testimony, Dr. Fein did not suggest the idea of a "low dose that is enabled [by sublingual administration]" [PX-15-2769] to Dr. Norgaard and his colleagues at Ferring. This

alone means that Dr. Fein did not himself invent "every feature" of the inventions claimed in the patents-in-suit. This conclusion is reinforced by the undeniable fact that Dr. Fein copied (sometimes *in haec verba*, sometimes thinly disguised) Ferring's research on low dose desmopressin in "his" patent applications, passing it off as his own.

During his consultancy at Ferring, Dr. Fein at most added to the concept of administering a lower dose of desmopressin to treat nocturia – an idea that many had conceived of before him – the notion that the ODT should be administered sublingually rather than supralingually. Even that idea had occurred to the scientists at Ferring some two years earlier. Dr. Fein's views (or Dr. Nardi's support for those views) may have convinced Ferring's scientists to follow his suggested route of administration, but Dr. Fein at most persuaded the Ferring desmopressin team to try something they had considered (but appear to have rejected) back in 1999.

The question then becomes whether Dr. Fein made a contribution to the overall invention that was significant enough to warrant his being listed even as one of the inventors on the patents in suit. My colleague Judge Castel concluded, in a lawsuit in which Serenity sought to have Dr. Fein listed as co-inventor on certain desmopressin-based patents owned by Ferring, that Serenity and Reprise had not presented clear and convincing evidence that, "Fein conceived of the concepts of lower does or the sublingual route of administration." [*Allergan*, ¶ 122; 135-142.] While that conclusion is not collateral estoppel in this case, where the patents are different and the burden of proof is on Ferring rather than Serenity/Reprise, it is highly persuasive for the proposition that Dr. Fein did nothing more than call a certain known concept (sublingual administration of a drug) to the attention of his colleagues (who were already testing the low dose hypothesis delivered via "melting" in the mouth) and argue for its adoption.

But I need not go so far. In its original patent application in Great Britain, Ferring elected to list Dr. Fein as one of several inventors; his contribution was specifically limited to "sublingual absorption" by Ferring's patent attorney. This was consistent with the only inventive concept Dr. Fein had claimed (on behalf of himself and Dr. Nardi, an admission that this court finds highly significant) in the inventorship memorandum that he wrote in May of 2002 – prior to the parties' falling out and the end of his consultancy.[26] When relations soured and Dr. Fein started asserting his rights to an invention – originally limited to sublingual absorption and without any low dose or plasma concentration feature – Ferring did not contest the matter, but simply eliminated the route of administration from its patent application and removed Dr. Fein's name as an inventor.[27] Treating Ferring's behavior as an admission that Dr. Fein's (and Dr. Nardi's) contribution to this effort was not *de minimis*, it nonetheless establishes, by more than clear and convincing evidence, that the Dr. Fein was not the sole inventor of everything he now claims to have invented all by himself. He is, at best, one of many fathers of the concepts that underlie the patents-in-suit – and far from the most significant.

VERDICT

The verdict on the counterclaims is for Ferring, the Counterclaim Defendants.

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[26] I do not accept Dr. Fein's testimony that he mentioned Dr. Nardi only as a professional courtesy [Trial Tr. 1260:13-1261:16.]; it is perfectly obvious, to this Court at least, that Dr. Nardi was dropped as a co-inventor by Dr. Fein when he applied for his patents because Nardi was a senior Ferring employee who owed a fiduciary duty to Ferring, and all of his intellectual property belonged to his employer. That Dr. Fein found a way for Dr. Nardi to profit from the commercialization of the patents-in-suit notwithstanding this impediment – by giving him an interest in Serenity/Reprise – suggest to me that Dr. Nardi had rather more to do with this than Dr. Fein is willing to admit.

[27] That Ferring justified its actions by asserting that the concept Dr. Fein had claimed as his own was already in the public domain is understandable in light of the evidence, but the timing of its move was clearly an attempt to avoid precisely what has occurred – years of litigation with Dr. Fein over desmopressin.

The Clerk of Court shall enter judgment accordingly dismissing the counterclaims, with costs to the Counterclaim Defendants, and then shall close the file.

Dated: August 21, 2020

Chief Judge

BY ECF TO ALL COUNSEL